Third Edition
Second Revision
January 2022

DRUG REGISTRATION GUIDANCE DOCUMENT (DRGD)

Bahagian Regulatori Farmasi Negara (NPRA)
Ministry of Health

GUIDELINE HISTORY

No.	Guideline	Description of Amendment	Effective date
1.	a) Guidelines for Application for Registration of Pharmaceutical Products, Third Edition b) *Permohonan Pendaftaran Keluaran Ubat Tradisional*, Second Edition	Initial Publication *(only available in hardcopy)*	a) October 1993 b) December 1998
2.	Drug Registration Guidance Document (DRGD)	Merger of 1(a) and 1(b) *(DRGD was first made available on the NPRA website starting from this version)*	2004
3.	Drug Registration Guidance Document (DRGD), First Edition - January 2013	• Major revision and comprehensive updates to the DRGD • Restructuring and renumbering of the Appendices	1 January 2013
4.	Drug Registration Guidance Document (DRGD), Second Edition – September 2016	Major revision due to NPRA name change from Biro Pengawalan Farmaseutikal Kebangsaan (NPCB) to Bahagian Regulatori Farmasi Negara (NPRA) in July 2016	1 September 2016

No.	Guideline	Description of Amendment	Effective date
5.	Drug Registration Guidance Document (DRGD), Third Edition – January 2021	• Major revision due to NPRA restructure on 2 December 2019 • Restructuring and renumbering of the Appendices • The main body of the DRGD (62 pages) and its appendices can be downloaded separately from the NPRA website for easy viewing. • List of DRGD updates will be published with the DRGD on the NPRA website.	31 January 2021

This guidance document is issued by the Director of Pharmaceutical Services under Regulation 29,
Control of Drugs and Cosmetics Regulations 1984.

NPRA reserves the right to amend any part of the guidance document as it deems fit.

Bahagian Regulatori Farmasi Negara (NPRA)

Lot 36, Jalan Universiti (Jalan Profesor Diraja Ungku Aziz),
46200 Petaling Jaya,
Selangor Darul Ehsan, Malaysia

Tel: 603-7883 5400

Fax: 603-7956 2924, 7956 7075

E-mail: npra@npra.gov.my

Website: *https://www.npra.gov.my/*

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PREAMBLE

- This "**DRUG REGISTRATION GUIDANCE DOCUMENT (DRGD)**" will serve as the reference guide for the registration process including quality control, inspection & licensing and post-registration activities of medicinal products.

- This DRGD shall be read in conjunction with the current laws and regulations together with other relevant legislations, where applicable, governing pharmaceutical and natural products for human use in Malaysia, which include but are not limited to the following:

  a) Sale of Drugs Act 1952;
  b) Control of Drugs and Cosmetics Regulations 1984;
  c) Dangerous Drugs Act 1952;
  d) Poisons Act 1952;
  e) Medicines (Advertisement & Sale) Act 1956;
  f) Wildlife Conservation Act 2010 (Laws of Malaysia Act 716); and
  g) International Trade in Endangered Species Act 2008 (Act 686)

  The written laws shall take precedence over this guidance document in any event of discrepancy.

- The <u>scope</u> of this DRGD includes information relating to administrative requirements and procedures for:
  a) Submission of an application for the registration of medicinal products, which is based on the ASEAN Common Technical Dossier/ Requirements (ACTD/ ACTR), where applicable;
  b) Submission of an application for the licensing of manufacturers, importers and wholesalers;
  c) Submission for amendments to a registered medicinal product; and
  d) Post-registration activities.

- This DRGD contains five (5) Main Sections and thirty-four (34) Appendices. The main sections are :
  a) Section A: General Overview
  b) Section B: Product Registration Process
  c) Section C: Quality Control
  d) Section D: Inspection, Licensing, Certificate
  e) Section E: Post-Registration Process

- Applicants shall familiarize themselves with the contents of this guidance document and the governing legislations before they submit applications for medicinal product registration.

- The Authority may request for information or specify conditions not described in this document that is deemed necessary to ensure the quality, safety and efficacy of the product.

- Ongoing review of regulatory policies will continue taking into account the global regulatory environment, to allow for timely and pertinent changes.

- For more information, please refer to Directives issued by the Senior Director of Pharmaceutical Services and NPRA Circulars.

- Applicants are advised to refer to the NPRA website for the latest updates of the DRGD and other related guidelines.

- **Separate guidelines** are available for Cosmetics and Veterinary products at the NPRA website.
  For cosmetics, refer to Guidelines for Control of Cosmetic Products in Malaysia
  For veterinary products, refer to Registration Guideline of Veterinary Products (REGOVP)

- The Authority reserves the right to amend any part of the DRGD as it deems fit.

- Any enquiry on registration of products may be submitted to:

  Secretary,
  Drug Control Authority,
  National Pharmaceutical Regulatory Agency,
  Ministry of Health Malaysia,
  Lot 36, Jalan Universiti (Jalan Profesor Diraja Ungku Aziz),
  46200 Petaling Jaya, Selangor.

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ABBREVIATIONS AND ACRONYMS

ACCSQ-PPWG	ASEAN Consultative Committee on Standards and Quality - Pharmaceutical Product Working Group
ACTD	ASEAN Common Technical Dossier
ACTR	ASEAN Common Technical Requirement
AMV	Analytical Method Validation
ANOVA	Analysis of Variance
API	Active Pharmaceutical Ingredient *Interchangeable with drug substance or active substance*
ASEAN	Association of Southeast Asian Nations
ATC	Anatomical Therapeutic Chemical
BA	Bioavailability
BE	Bioequivalence
BET	Bacterial Endotoxins Test
BMF	Batch Manufacturing Formula
BP	British Pharmacopoeia
BSE	Bovine Spongiform Encephalopathy
CDCR	Control of Drugs & Cosmetics Regulations 1984
CEO	Chief Executive Officer
CEP	Certificate of Suitability *CEP is referring to Certificate of Suitability of European Pharmacopoeia monographs issued by the EDQM*
CFC	Chlorofluorocarbons
CFS	Certificate of Free Sales
CI	Confidence Interval
CMC	Chemistry, Manufacturing and Controls
CoA	Certificate of Analysis
COH	Change of Product Registration Holder *Previously known as Change of Marketing Authorization Holder*
COMBO	Combination Pack
COS	Change of Manufacturing Site
CPP	Certificate of Pharmaceutical Product
CTX	Clinical Trial Exemption
CTIL	Clinical Trial Import License

DCA	Drug Control Authority
DE	Data Exclusivity
DMF	Drug Master File (interchangeable with Active Substance Master File)
DNA	Deoxyribonucleic acid
DRGD	Drug Registration Guidance Document
EDQM	European Directorate for the Quality of Medicine and Healthcare
ELC	Endotoxin Limit Concentration
EMA	European Medicines Agency
EP	European Pharmacopoeia
FDA	Food and Drug Administration
FDI	Food-Drug Interphase
FEO	For Export Only
FPQC	Finished Product Quality Control
FSQD	Food Safety and Quality Division
FTIR	Fourier Transform Infrared
g	gram
GABA	Gamma-Amino Butyric Acid
GC	Gas Chromatography
GCP	Good Clinical Practice
GDP	Good Distribution Practice
GMP	Good Manufacturing Practice
HACCP	Hazard Analysis and Critical Control Point
HBsAg	Surface Antigen of the Hepatitis B Virus
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
HPLC	High Performance Liquid Chromatography
HS	Health Supplement
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INN	International Non-proprietary Names
IPQC	In-Process Quality Control
ISO	International Organization for Standardization

JAKIM	Malaysia Department of Islamic Development *(Jabatan Kemajuan Islam Malaysia)*
JP	Japanese Pharmacopoeia
L	Litre
LAL	Limulus Amebocyte Lysate
LOA	Letter of Authorization
LOC	Letter of Commitment
LOI	Letter of Intent
mAb	monoclonal antibody
MaV	Major Variation
max	maximum
MCB	Master Cell bank
MDDCI	Medical Device-Drug-Cosmetic Interphase
MiV-PA	Minor Variation Prior Approval
MiV-N	Minor Variation Notification
mL	millilitre
MPN	Most-Probable Number
MSM	Methylsulphonylmethane
MVD	Maximum Valid Dilution
NAT	Nucleic Acid Testing
NCE	New Chemical Entity
NDP	New Drug Product
NMT	Not More Than
NPRA	National Pharmaceutical Regulatory Agency
NRV	Nutrient Reference Value
OTC	Over-the-Counter
PBRER	Periodic Benefit-Risk Evaluation Report
Ph. Eur.	European Pharmacopoeia
PI	Package Insert
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PKKK	Centre of Compliance and Quality Control *PKKK refers to Pusat Komplians dan Kawalan Kualiti*
PKPSR	Centre of Regulatory Coordination and Strategic Planning *PKPSR refers to Pusat Koordinasi dan Perancangan Strategik Regulatori*

PMF	Plasma Master File
POA	Protocol of Analysis
PPPK	Centre of Product and Cosmetic Evaluation *PPPK refers to Pusat Penilaian Produk dan Kosmetik*
ppm	parts per million
PRH	Product Registration Holder *(Previously known as Marketing Authorization Holder, MAH)*
PV	Process Validation
RiMUP	Consumer Medication Information Leaflet RiMUP refers to Risalah Maklumat Ubat untuk Pengguna *(Previously known as Patient Information Leaflet or PIL)*
RNA	Ribonucleic acid
RSD	Relative Standard Deviation
SIRIM	Standards and Industrial Research Institute of Malaysia
SPC	Summary of Product Characteristics
spp.	Species
Syn.	Synonym
TAMC	Total Aerobic Microbial Count
TGA	Therapeutic Goods Administration
TLC	Thin Layer Chromatography
TSE	Transmissible Spongiform Encephalopathies
TYMC	Total Yeasts and Molds Count
USP	United States Pharmacopeia
USPI	US Package Insert
UV	Ultra-Violet
VVM	Vaccine Vial Monitor
WCB	Working Cell Bank
WHO	World Health Organization

GLOSSARY

Bulk Product: A product that has completed all processing stages up to, but not including, final packaging

Contract Manufacturer: Any person who manufactures any product on the order of another person to whom a manufacturer's licence has been issued under these Regulations (*as defined in Regulation 2, CDCR 1984*)

Finished Product: A product that has undergone all stages of production and quality control, including packaging in its final container and labelling

Indigenous Medicine: A system of treatment and prevention of disease established through traditional use of naturally occurring substances (*as defined in Regulation 2, CDCR 1984*)

Licensed Importer: A person to whom an import license has been issued under Regulation 12, CDCR 1984 (*as defined in Regulation 2, CDCR 1984*)

Licensed Manufacturer: A person to whom a manufacturer's licence has been issued under these Regulations, and includes a contract manufacturer (*as defined in Regulation 2, CDCR 1984*)

Licensed Wholesaler: A person to whom a wholesaler's license has been issued under Regulation 12, CDCR 1984 (*as defined in Regulation 2, CDCR 1984*)

Manufacturer: A person carrying out one or more of the steps specified in the definition of manufacture

Manufacture, in relation to any product includes –

a) The making or assembling of the product;
b) The enclosing or packing of the product in any container in a form suitable for administration or application, and the labelling of the container and;
c) The carrying out of any process in the course of any of the foregoing activities.
(*as defined in Regulation 2, CDCR 1984*)

Medicinal Product: The term refers to 'product' as stated in Regulation 2, CDCR 1984, which is applicable to pharmaceutical and natural products

OTC: Refers to Generic products (Non-Scheduled Poison)

Product Owner: A person, company or entity who is the legal/ registered owner of the product formulation and/or process with whom the marketing authorization holder has a contract *(glossary used in ACTD and ACTR)*

Product Registration Holder: The company or corporate or legal entity in the field of pharmaceuticals who has been granted the marketing authorization. This party is responsible for all aspects of the product, including quality and compliance with the conditions of marketing authorization. The authorized holder must be subjected to legislation in the country that issued the marketing authorization, which normally means being physically located in that country *(glossary used in ACTD and ACTR)*.

Repacker: Please refer to **Appendix 33: Explanatory Notes for Repackers**

The Authority: Refers to Drug Control Authority (DCA)

The System: Refers to QUEST system

SECTION A: GENERAL OVERVIEW

1. INTRODUCTION

The Control of Drugs and Cosmetics Regulations (CDCR) 1984 were promulgated under the Sale of Drugs Act 1952. The Authority (known as Drug Control Authority, DCA) established under these Regulations, is tasked with ensuring the quality, safety and efficacy of medicinal products through the registration, including quality control, inspection, licensing and post-registration activities. The National Pharmaceutical Regulatory Agency (NPRA) acts as the secretariat to the Authority.

Under the CDCR 1984, Regulation 7(1): *Except as otherwise provided in these Regulations, no person shall manufacture, sell, supply, import, possess or administer any product unless:*
(a) the product is a registered product; and
(b) the person holds the appropriate licence required and issued under these Regulations.

2. PRODUCT DEFINITION

Under the CDCR 1984, Regulation 2: **"*Product*"** means:
(a) a drug[1] in a dosage unit or otherwise, for use wholly or mainly by being administered to one or more human beings or animals for a medicinal purpose[2]; or
(b) a drug[1] to be used as an ingredient of a preparation for a medicinal purpose[2].

Under Sales of Drug Act 1952, Section 2:

[1] **"*drug*"** includes any substance, product or article intended to be used or capable, or purported or claimed to be capable, of being used on humans or any animal, whether internally or externally, for a medicinal purpose.

[2] **"*medicinal purpose*"** means any of the following purposes:

(a) alleviating, treating, curing or preventing a disease or a pathological condition or symptoms of a disease;
(b) diagnosing a disease or ascertaining the existence, degree or extent of a physiological or pathological condition;
(c) contraception;
(d) inducing anaesthesia;
(e) maintaining, modifying, preventing, restoring, or interfering with, the normal operation of a physiological function;
(f) controlling body weight;
(g) general maintenance or promotion of health or wellbeing.

Note:
In the DRGD, the term "medicinal product" refers to the term "product" as stipulated in Regulation 2, CDCR 1984.

3. PRODUCT CLASSIFICATION

It is important to determine the category of a product whether it meets the definition in **2. Product Definition** because different regulatory requirements may apply.

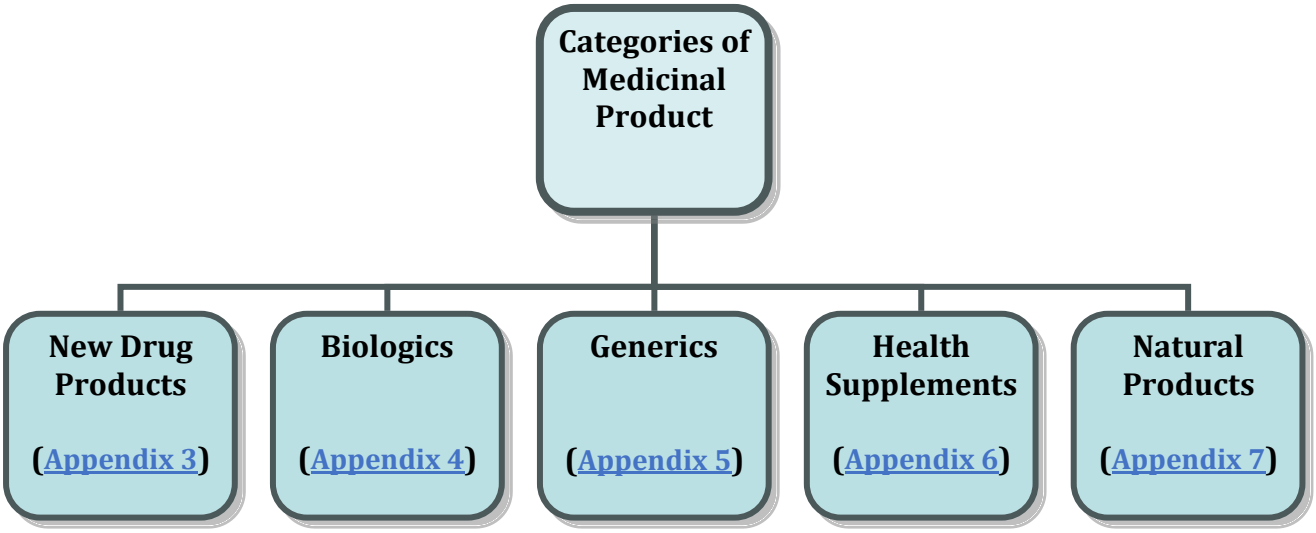
Applicant may submit a classification form, which can be downloaded from the NPRA website, if unsure of the product category.

For products related to:

a) Food - Drug Interphase (FDI), refer to **Appendix 1: Food-Drug Interphase (FDI) Products**

b) Medical Device - Drug - Cosmetic Interphase (MDDCI), refer to **Appendix 2: Medical Device-Drug-Cosmetic Interphase (MDDCI) and Combination Products**

Medicinal product shall be registered with the Authority under the following categories:



4. EXEMPTIONS FOR PRODUCTS NOT REGISTERED WITH THE AUTHORITY

4.1 Products not registered with the Authority and are intended to be manufactured locally for the purpose of clinical trial require a Clinical Trial Exemption (CTX) from the Director of Pharmaceutical Services.

4.2 For more information pertaining to products to be used in clinical trial, please refer to **The Malaysian Guideline for Application of Clinical Trial Import License & Clinical Trial Exemption**.

4.3 Any person who wishes to manufacture any product solely for the purpose of producing a sample for registration should apply for an exemption for the manufacture of sample. (This applies to locally manufactured products only)

4.4 The exemptions mentioned in 4.1 and 4.3 above are in accordance with Regulation 15(5), CDCR 1984: "Any person who wishes to manufacture any product solely for the purpose of producing samples for clinical trials, for registration or issuance of notification note under these Regulation may on application be exempted by the Director of Pharmaceutical Services from the provisions of regulation 7 (1) or regulation 18A".

4.5 For more information on exemptions for products, refer to Regulation 15, CDCR 1984: Exemptions & Saving.

5. APPLICATION PROCEDURES

5.1 Who Shall Apply for Product Registration

a) The applicant for product registration, known as the Product Registration Holder (PRH), must be a locally incorporated company, corporate or legal entity, with permanent address and registered with the Companies Commission of Malaysia (SSM) (with business scope related to health/ pharmaceutical product).

b) The name of the PRH, including product manufacturer, shall not reflect the following:
   (i) Name of a government agency
   (ii) Name of an institute of higher education/ research
   (iii) Any name that reflects the quality of pharmaceutical products
   e.g. "*Amalan Perkilangan Baik (APB)*", Good Manufacturing Practice (GMP)
   (iv) Name of a disease
   (v) Name of an organ
   e.g. Heart, Brain, Kidney etc.

c) If the applicant is not the product owner, the product owner shall authorize the PRH in writing to be the holder of the product registration who is responsible for all matters pertaining to the quality, safety and efficacy of the product. This includes the responsibility to update any information relevant to the product / application.

d) Refer to **Appendix 8: Supplementary Documentation (Particulars of Product Owner and Manufacturer)**.

5.2 Responsibilities of the Applicant

a) The PRH must ensure that all transactions with NPRA are done by their appointed person(s).

b) Failure to make payment within thirty (30) days from the date of approved screening shall result in rejection of the application.

c) For the purpose of product registration, the PRH shall conform to the following:
   (i) The PRH shall comply with all legal provisions in Malaysia;
   (ii) The government/ authority is not liable for any offence committed by the PRH as a result of any breach of any law; and
   (iii) The PRH shall indemnify the government if any claim is made against the government as a result of any breach of any law by the applicant whether intentionally or otherwise;

d) The PRH is responsible for all quality, safety and efficacy information submitted in support of the product registration application; and shall inform the Authority in a timely manner regarding any change in product information during the course of evaluation.

   This is in accordance with Regulation 8(9) CDCR 1989: "Any person who knowingly supplies any false or misleading information to the Authority with his application for the registration of a product commits an offence".

e) The PRH is responsible for responding and providing feedback for requested supplementary data / information, documentation or samples by the Authority within the specified time frame. If the applicant is unable to submit the requirements within the specified time frame, a written request for an extension shall be submitted to NPRA.

f) The application shall be rejected if the applicant fails to submit required supplementary data / information or documentation within six (6) months from the first correspondence date.

g) The PRH is responsible for all matters pertaining to the quality, safety and efficacy of the registered product, including:

   (i) Data updates on product quality, safety and efficacy or current Good Manufacturing Practice (cGMP) compliance of the manufacturers (and repackers, where applicable).

   This is in accordance with Regulation 8(5) CDCR 1984: "Any change in any document, item, sample, particulars or information shall be notified in writing by the applicant to the Authority within fourteen (14) days from the date of such change".

   (ii) Any decision to withdraw the registration of the product with reasons.

h) The PRH shall supply such documents, items, samples, particulars or information as the Authority may require in relation to the registered product.

i) No change in name, composition, characteristics, origin, specifications, manufacturer, packing, indications, labelling, package insert, product literature or any relevant particulars of the registered product shall be made without prior approval of the Authority.

j) The PRH must notify the Authority of any change in correspondence details, including the name, address, contact person, telephone number, fax number and email.

k) The PRH must notify the Authority immediately upon cessation of the applicant as the product registration holder.

5.3 How to Apply

a) For registration of products, only web-based online submissions via the QUEST system at *https://quest3plus.bpfk.gov.my/front-end/login-chrome.php* shall be accepted.

b) To conduct transactions via the QUEST system, the applicant must first register for a QUEST membership with NPRA and purchase a USB Token that contains a User Digital Certificate, from MSC Trustgate.com Sdn. Bhd., which shall be installed in the applicant's computer.

c) For further details, refer to the *Frequently Asked Questions* on QUEST System.

d) For charges regarding the QUEST USB token, refer to **Appendix 9: Fees**.

e) The applicant is responsible for any act of fraudulence or misuse pertaining to its authorized QUEST USB token(s).

f) NPRA reserves the rights to approve or reject any application for QUEST membership.

5.4 Fees

a) This is in accordance with Regulation 8(3): "The Authority may charge any applicant such costs as it may incur for the purpose of carrying out any evaluation or investigation prior to the registration of any product".

b) Refer to **Appendix 9: Fees** for fees imposed.

c) Applications submitted without the correct fees will not be processed.

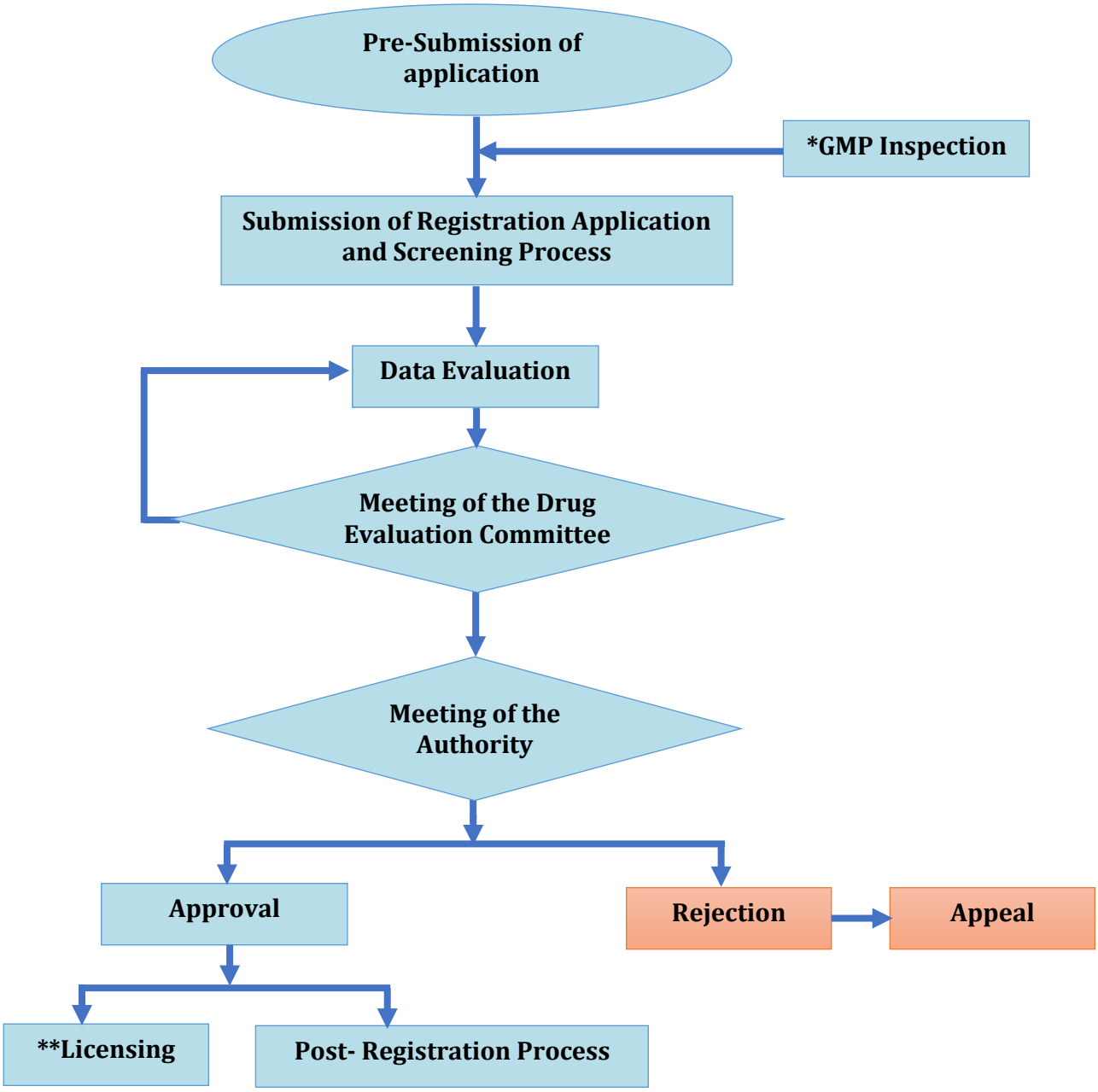
d) Payment of the processing fee and any other charges shall be done online through the QUEST system (FPX/ credit card) or in the form of bank draft/ banker's cheque/ money order/ postal order made payable to **"Biro Pengawalan Farmaseutikal Kebangsaan"**.

e) A separate payment is required for each application.

f) Any payment made shall NOT BE REFUNDABLE once the application has been submitted and payment is confirmed.

SECTION B: PRODUCT REGISTRATION PROCESS

The process of product registration ensures that pharmaceutical products are evaluated for its safety, efficacy and quality, whereas natural products are evaluated for its safety and quality, prior to registration by the Authority and release into the market.



* Good Manufacturing Practice (GMP) Certification
** Application for Manufacturer's, Import and/or Wholesaler's License

6. PREPARATION FOR SUBMISSION OF APPLICATION

It is important for the applicant to consider the following when registering a product:

(a) Knowing which type of application to apply for;
(b) Knowing which evaluation route to choose; and
(c) Arranging for a Pre-Submission Meeting (PSM) with NPRA for advice, if required.
For further information, refer to **Guidance Document for Pre-Submission Meeting (PSM)** in the NPRA website.

6.1 Category of Product

The applicant shall first determine the category of product as described under **3. Product Classification** because different product categories require different data.

If the applicant is unable to determine the product category, they may submit a Classification Form to NPRA for verification.

6.2 Data Exclusivity

Data exclusivity refers to protection of undisclosed, unpublished and non-public domain pharmaceutical test data, the origination of which involves considerable effort, submitted as required to the Director of Pharmaceutical Services for the purpose of scientific assessment in consideration of the:

a) Quality, safety and efficacy of any **new drug product** containing a New Chemical Entity
b) Safety and efficacy for a second indication of a registered drug product as a condition for registration of any new drug product containing a New Chemical Entity; or approval for a **second indication of a registered drug product**

For information pertaining to Register of Data Exclusivity Granted in Malaysia, refer to Register of Data Exclusivity Granted in Malaysia (New Drug) and Register of Data Exclusivity Granted in Malaysia (Second Indication). Please also refer to **Appendix 10: Data Exclusivity**.

6.3 Type of Application

The type of application for product registration depends on the category as specified in the respective appendix:

Appendix 3: Guideline on Registration of New Drug Products
Appendix 4: Guideline on Registration of Biologics
Appendix 5: Guideline on Registration of Generics
Appendix 6: Guideline on Registration of Health Supplements
Appendix 7: Guideline on Registration of Natural Products
Appendix 7A: Homeopathic Products
Appendix 7B: Guideline on Natural Products with Therapeutic Claim

***Note:**
Refer to **Appendix 11: Regulatory Control of Active Pharmaceutical Ingredients (APIs)**
*Applicable for NDP and Generics

6.3.1 Application for Priority Review

Priority review may be granted for new product application (in the category of New Drug Products, Biologics and Generics), which fulfils the conditions. Refer to **Appendix 12: Priority Review**.

6.3.2 Registration of Combination Pack (Combo Pack)

Combination pack:

a) refers to products that are packed together in combination for a therapeutic regimen, such as for the treatment of *Helicobacter Pylori*, Hepatitis C, etc.

b) shall be registered as a single product.

c) must consist of registered products only**:**
   (i) If a combination pack consists of registered and unregistered products, the unregistered product needs to be registered first, prior to submission of the application;
   (ii) If a combination pack consists of registered products from different product owners/ PRH, letters of authorization from each product owner, which include product name and product registration number, shall be submitted.

Combination pack is not applicable for:

(i) products packed together in combination NOT FOR THERAPEUTIC REGIMEN, but for the convenience of consumers (e.g. capsules of five health supplement products in a blister pack)
(ii) products packed together with diluent(s)/ adjuvant(s)

Labelling requirements specific for combination pack are shown below:

Outer Label	Immediate Label
Name of combination pack	Individual name for each product OR name of combination pack
Registration number for the combination pack	Individual registration number for each product OR registration number for combination pack
Name and address of manufacturer and product registration holder	Name and address of manufacturer and product registration holder
Batch number of the combination pack product	Individual batch number for each product
Expiry date (according to the shortest expiry date among the individual products)	Individual expiry date for each product

6.3.3 Registration of For Export Only (FEO) Product

a) For Export Only (FEO) product refers to locally manufactured products for exporting purpose only and not marketed locally.

b) This does not apply to imported products meant to be packed/repacked locally and to be re-exported. (This application falls under Regulation 7(2)(b), CDCR 1984. A separate *application form* may be obtained from the NPRA website)

c) Applications for registration of FEO products are only accepted under the following condition(s) and must be supported with evidence issued by the competent Authority of the importing countries (self-declaration is not accepted):
   (i) Countries that do not impose the same specific regulatory requirements as Malaysia (e.g. formulation with banned/ prohibited ingredients, Zone IVb stability study, bioavailability/ bioequivalence study, API evaluation, etc.); OR
   (ii) Countries that have different requirements such as different formulation (e.g. colour or strength of ingredients), shape or manufacturing process, etc. as compared to a registered product; OR
   (iii) Difference in classification category of the products (e.g. as food in the importing country) for health supplements and natural products (Traditional and Homeopathic Medicines).

d) Applications for registration of FEO products are processed based on abridged evaluation. However, the following additional requirements must be fulfilled for pharmaceutical products. It is not applicable to health supplements and natural products (Traditional and Homeopathic Medicines):
   (i) Certificate of Analysis (CoA) of finished product for at least 1 pilot batch; AND
   (ii) Minimum 6 months stability data (real time and accelerated stability study) for at least 1 pilot batch.

e) Application is made via online submission in the QUEST system.

f) Applicant may apply for a Certificate of Pharmaceutical Product (CPP) for registered FEO products.

g) For a registered product intended for exportation as well as to be sold in Malaysia:
   (i) A new application for registration for export only will NOT be required if there is no change in the formulation and appearance of the registered product
   (ii) The applicant may apply for a CPP for the registered product and with an explanation/ declaration letter on any difference(s) (e.g. a product exported with a different product name) to the importing country

Reference:
Bil. (11)dlm.BPFK/07/25 Jld.2
Arahan Pengarah Kanan Perkhidmatan Farmasi Bil. 11 Tahun 2018: Direktif Kaji Semula Pendaftaran Produk Untuk Tujuan Eksport Sahaja (FEO) (6 March 2018)

6.3.4 Designation and Registration of Orphan Medicines

Refer to **Appendix 13: Designation and Registration of Orphan Medicines**

6.3.5 Variants

a) Variants refer to products with differences in terms of fragrance/ flavour/ colour.

b) The requirements to support an application for variant are based on the category of products.

c) To register a variant:
   (i) The variants should only differ in terms of fragrance/ flavour and colour.
   (ii) Product name of the variants shall remain the same, with the addition of an identifying variant name.
   (iii) Each variant shall be registered as one (1) product with a different registration number.

d) Variants to the registered product may be considered for the following dosage forms:

(i) Products Containing Scheduled Poison
ONLY for pediatric oral liquid preparations

(ii) Products Containing Non-Scheduled Poison
Lozenges, Chewable tablets, Effervescent powders/ tablets, Powder, Granule, Oral liquid, Dental preparations (rinses, dentifrices), Medicated soaps (bar, liquid), Vaginal creams and douches, Topical Liquid

6.3.6 Multiple Applications

A separate application for product registration shall be required for each product for the following conditions:

(i) Products containing the same ingredients but made to different specifications, in terms of strength/ content of ingredient(s), dosage form, description, etc.; or
(ii) Different manufacturer

However, different packaging (materials) or pack sizes (quantity/ volume) of a product made by the same manufacturer to the same specifications, formulation and dosage form (including parenteral preparations, peritoneal dialysis fluids and haemofiltration solutions introduced into human bodies) shall require only ONE application for product registration. The product registration shall be for the packaging and pack sizes stated in the registration documents only.

Note:
Registration application of **the same product in all aspects** with different product names:
a) by the **same PRH** is **not allowed** by the Authority
b) by **different PRH** **may be considered** by the Authority with **acceptable justification**

Product name must comply with the requirements in **7.3 Product Name.**

6.3.7 Second or Third Source

a) It is defined as a product that is the same as the product from the first source in all aspects, except for the site of manufacture.

b) An application for a second source may be considered by the Authority but only with justification provided.

c) A second source product, excluding biologic products, may differ in the following aspects:
   (i) equipment/ machines;
   (ii) minor manufacturing process (e.g. blending time, number of sub-parts);
   (iii) batch size;
   (iv) packaging materials, thickness of same packaging materials, pack sizes;
   (Note: Use of different packaging materials shall be supported with stability study report)
   (v) manufacturer of API; and
   (vi) source of excipients

d) Differences in shape, embossment and thickness of tablet are NOT permitted to avoid changes in product identity and to prevent subsequent confusion.

e) For pharmaceutical products, no third source is allowed for the same product, unless in emergency situations such as an outbreak of infectious disease.

f) The manufacturer shall declare with supporting manufacturing validation process data that there is no change in formulation, specification of active ingredient(s) and excipient(s), and the finished product for the second source product compared to the first source. There should be no difference in product identity and presentation, to avoid confusion.

g) Biologics are highly sensitive to manufacturing condition. If any of the conditions outlined below are not fulfilled, the application is automatically considered as a new application:

   (i) The proposed facility is approved for manufacturing activities for the same company/ sponsor
   (ii) No change in the composition, manufacturing process and drug substance as well as drug product specifications
   (iii) No change in the container/ closure system
   (iv) The same validated manufacturing process is used
   (v) The newly introduced product is in the same family of product(s) or therapeutic classification as those already approved at the site and uses the same filling process/ equipment
   (vi) Only one Final Release Site

6.4 Evaluation Routes

The method of evaluation for the registration of a product is divided into **four (4) types**:

a) Full Evaluation (Standard Pathway)
b) Full Evaluation (Conditional Registration)
c) Full Evaluation via Abbreviated and Verification Review
d) Abridged Evaluation

Refer to **Appendix 14: Evaluation Routes**.

7. REGULATORY REQUIREMENTS

Applicant shall comply with all of the following requirements prior to submitting a registration application. Failure to do so shall result in the rejection of the application by the Authority.

Note: Please also refer to guidelines for the respective product category at:

Appendix 3: Guideline on Registration of New Drug Products
Appendix 4: Guideline on Registration of Biologics
Appendix 5: Guideline on Registration of Generics
Appendix 6: Guideline on Registration of Health Supplements
Appendix 7: Guideline on Registration of Natural Products
Appendix 7A: Homeopathic Products
Appendix 7B: Guideline on Natural Products with Therapeutic Claims
Appendix 11: Regulatory Control of Active Pharmaceutical Ingredients (APIs)

7.1 Requirements for Full Evaluation and Abridged Evaluation

Data required to be submitted for full evaluation or abridged evaluation is based on the product category.

Refer to **Appendix 15: Requirements for Full Evaluation and Abridged Evaluation**.

7.2 Bioequivalence (BE) Requirements

Requirements for BA/ BE study applicable to generics products are specified in **Appendix 16: Bioequivalence (BE) Requirements**.

7.3 Product Name

a) Product name is defined as a name given to a product, which may either be a proprietary name (an invented name); or a generic name (common name) or scientific name, together with a trade mark or the name of the manufacturer.

b) Product name shall consist of dosage form and strength (for single active ingredient product) (e.g. X Brand Paracetamol Tablet 500mg).

c) Dosage form and strength of product would need to be entered as part of product name to allow for multiple dosage forms (e.g. tablet, capsule) and strengths (e.g. 200mg and 400mg) for any particular named (proprietary or generic) product.

d) The generic name is the international non-proprietary name recommended by WHO (rINN), or if one does not exist, the usual approved name. The generic name cannot be used alone as the product name, but can be used in combination with another name, other than the generic name.

e) The invented name shall not pose any risk of confusion with the common name.

f) Font size of the product name on the label, including alphabets and numbers, shall be equal in size.

g) Product name shall not suggest the following:
   i. Tricky, confusing and against the law;
   ii. Scandalous and offensive;
   iii. Prejudicial;
   iv. Notorious

h) If a product name is found to be similar in terms of spelling and pronounciation to another registered product or any other name deemed inappropriate by the Authority, NPRA reserves the rights to request for the change of the product name.

i) Any product name that is the same or similar either in writing/ pronunciation with the product name of an adulterated product or a product that has been revoked due to safety concerns is prohibited.

j) The product name shall be shown on the product labelling, i.e. immediate label, outer unit carton, package insert and consumer medication information leaflet.

k) Product names not permitted to be registered are listed in **Appendix 17: Product Names Not Permitted to Be Registered**.

l) Additional references:
   - **Appendix 6: Guideline on Registration of Health Supplements** 5.1.1 List of Non-Permissible Product Name for Health Supplement Products
   - **Appendix 7: Guideline on Registration of Natural Products**, Table 1: Non-Permissible Product Names

7.4 Ingredients

Refer to **Appendix 18: List of Permitted, Prohibited and Restricted Substances**.

7.5 Indications

The registered product shall only be indicated for use as approved by the Authority. The PRH may exclude any indication(s) protected by patents or exclusivities.

Indications other than those specified and accepted at the time of registration must not be included in any product literature, data sheets, package inserts, labels, etc. without prior permission of the Authority.

7.6 Labelling Requirements

The PRH shall ensure that the product label complies with the labelling requirements defined in:

- **Appendix 19: General Labelling Requirements**
- **Appendix 20: Specific Labelling Requirements.**
  This Appendix includes the **List of Substances That Requires Specific Labelling Requirements** (statement to be included in the label, package insert, RiMUP)

7.7 Special Conditions for Registration of a Particular Product or Group of Products

The importation, manufacture, sale and supply of the registered product shall comply with all specific conditions imposed by the Authority as listed in **Appendix 21: Special Conditions for Registration of a Particular Product or Group of Products**.

7.8 Educational Materials

As part of risk minimization measures, the PRH shall provide educational materials to healthcare professionals and patients in reducing risk(s) for a particular product.

This applies to products containing active ingredient such as:

(i) Sodium Valproate

(ii) Retinoids

Refer to **Appendix 22: Educational Materials**.

7.9 Packaging

7.9.1 Shrink wrapping

Shrink wrapping of multiple boxes of approved pack sizes are allowed provided that the following conditions are met:

a) This refers to multiple boxes of approved pack sizes of a single or multiple registered products shrink wrapped and marketed together for the convenience of consumers.

b) This only applies to registered products from the Health Supplements, Natural Products (Traditional and Homeopathic Medicines) and Non-scheduled Poisons category (category T, N and X).

c) The shrink wrap does not come into contact with the dosage form.

d) There are no qualitative or quantitative changes to the approved registered primary packaging and the outer packaging.

e) The label contents of the product are not changed or obscured.

f) The shrink wrap used must be completely transparent and does not contain any stickers/ wordings/ graphics.

7.9.2 Starter Pack/ Patient Initiation Pack/ Dose Adjustment Pack

a) Such packs may consist of:

   (i) Combination of products with different strengths packed together in one packaging such as blister or calendar pack

   (ii) Combination of more than one pre-filled pens containing different strengths of preparation in one packaging

b) Must be registered under the same product owner and PRH.

c) Justified and proven specific dosing regimen shall be demonstrated through clinical studies.

d) Each product must be differentiated in terms of its physical description, e.g. colour, shape/size etc. to avoid confusion during drug administration.

e) For products in a calendar pack, additional beneficial criteria such as tablets of different strength may be arranged in order of the day of the week to assist patients.

f) Labelling requirements specific for starter pack/ patient initiation pack/ dose adjustment pack are shown below:

Outer Label	Immediate Label
• Statement of starter pack/ patient initiation pack/ dose adjustment pack • Individual name for each product	Individual name for each product
Both outer and immediate label must include: (i) Individual registration number for each product (ii) Name and address of manufacturer and product registration holder (iii) Individual batch number for each product (iv) Manufacturing date (according to the earliest manufacturing date among the individual product) (v) Expiry date (according to the shortest expiry date among the individual product)	

7.9.3 Patient Dispensing Pack

Scheduled poison or non-scheduled poison in tablet/ capsule, oral liquid preparation or dermatological preparation are required to comply with **Appendix 23: Patient Dispensing Pack for Pharmaceutical Products**.

7.10 Proposed Package Insert

Package insert (PI) is required for products containing scheduled poison and for injectable OTC products. PI may also be submitted for other OTC products. The draft copy of the PI shall be submitted for evaluation.

Sharing of PI is only allowed for products having the same active ingredient(s) but with different strengths.

The following information is required to be included in the PI:

a) Brand or Product Name
b) Name and Strength of Active Substance(s)
c) Product Description
d) Pharmacodynamics
e) Pharmacokinetics
f) Indication
g) Recommended Dosage
h) Route of Administration

i) Contraindications
j) Warnings and Precautions
k) Interactions with Other Medicaments
l) Pregnancy and Lactation
m) Side Effects
n) Symptoms and Treatment of Overdose
o) Effects on Ability to Drive and Use Machine
p) Preclinical Safety Data (*Not applicable for Generics*)
q) Instruction for Use (e.g., Incompatibilities - For injection only)
r) Storage Conditions (may be omitted if the information is stated on the label or outer carton labels)
s) Dosage forms and packaging available
t) Name and address of manufacturer/ product registration holder
u) Date of revision of PI

7.11 Consumer Medication Information Leaflet (RiMUP)

a) Consumer Medication Information Leaflet or *Risalah Maklumat Ubat untuk Pengguna (RiMUP),* is compulsory for products self-administered by patients, including:
   (i) Scheduled poisons (Category A);
   (ii) OTC products (Category X);
   (iii) Natural products with therapeutic claim; and health supplements with disease risk reduction claims.

b) The draft copy of the RiMUP in both English and *Bahasa Malaysia* shall be submitted for evaluation.

c) It is not compulsory for the RiMUP to be distributed with the product.

d) All approved RiMUP can be found in the NPRA website as reference for consumers. Healthcare professionals can retrieve and disseminate the RiMUP to patients if necessary.

e) For OTC products: If the product is intended to be sold without a PI or RiMUP, the information required to be included in the PI or RiMUP shall be printed on the unit outer-carton of the product. Submission of a soft copy of the RiMUP softcopy is still compulsory as mentioned above.

f) For further details, refer to:
   (i) *Bil. (15) dlm BPFK/PPP/01/03 Jilid 1 Arahan Pengarah Kanan Perkhidmatan Farmasi Bil. 5 Tahun 2011: Direktif Penguatkuasaan Keperluan Mengemukakan Risalah Maklumat Ubat untuk Pengguna (RiMUP)* (27 April 2011)
   (ii) *Garispanduan Pelaksanaan Risalah Maklumat Ubat untuk Pengguna (RiMUP)*

7.12 Product Authentication

The registered product shall be affixed with the security label (hologram) approved by the Authority. The said security label (hologram), which is serialized, shall be used to authenticate and verify that the product is registered with the Authority, and shall be affixed to the secondary packaging or immediate label of the product, whether locally manufactured or imported.

The security label (hologram) shall be affixed onto the secondary packaging of the product, (or, where there is no outer packaging, on the immediate label), on the front panel of the product label. The security label (hologram) shall cover none of the product particulars on the label.

Refer to:

a) **Appendix 19: General Labelling Requirements** where the security label (hologram) may be affixed on the product label;
b) FAQ on security label (hologram); and
c) Circulars and directives pertaining to security label (hologram):

Bil. (1)dlm.BPFK/PPP/07/25 Jld. 1
Arahan Pengarah Kanan Perkhidmatan Farmasi Bil. 2 Tahun 2013: Direktif Pelaksanaan dan Pengendalian Label Keselamatan (4 April 2013)

Bil. (17) dlm. BPFK/PPP/07/25 Jld. 3
Arahan Pengarah Kanan Perkhidmatan Farmasi Bil. 17 Tahun 2019: Penggunaan Label Keselamatan Baharu Dari Pembekal Yang Dilantik Oleh Kementerian Kesihatan Malaysia (KKM) (27 September 2019)

7.13 Language

All data and information including supporting documents for product registration such as certificates, letters and product labels shall be in English or *Bahasa Malaysia*.

7.14 *Halal* Logo

a) *Halal* logo may be used voluntarily on registered product label for the following categories, for both local and export market, provided that such products have been certified and approved *halal* by the Malaysia Department of Islamic Development (*Jabatan Kemajuan Islam Malaysia*, JAKIM):

(i) Non-scheduled poison, excluding veterinary products;

References:

Bil. (95)dlm.BPFK/PPP/01/03 Jld. 2

Penggunaan Logo Halal Bagi Produk Farmaseutikal Berdaftar Kategori Produk Bukan Racun (Over-The-Counter, OTC) (26 December 2012)

Bil. (6)dlm.BPFK/PPP/07/25

Arahan Pengarah Kanan Perkhidmatan Farmasi Bil. 7 Tahun 2013: Direktif Perluasan Skop Penggunaan Logo Halal Bagi Produk Farmaseutikal Berdaftar Kategori Produk Bukan Racun Berjadual Dalam Bentuk Parenteral (8 November 2013)

(ii) Health supplements;
(iii) Natural products; and
(iv) Cosmetics

b) The logo is **NOT** allowed to be used on the label of registered products other than the categories listed above.

c) Only *halal* logo issued by JAKIM or any Islamic Body recognized by JAKIM shall be accepted.

d) To use the halal logo on permitted product labels, which is not a mandatory requirement, the applicant is required to submit an application for consideration by the Authority.

e) The applicant shall submit an application for product registration variation to NPRA for approval to affix *halal* logo on the product label of a registered product, of which a *halal* certification has been granted. A copy of the *halal* certificate must be submitted as a supporting document.

7.15 Directives

The Senior Director of Pharmaceutical Services may issue written directives or guidelines to any person or a group of persons as he thinks necessary for the better carrying out of the provisions of these Regulations and which in particular relate to:

(i) Product quality, safety and efficacy;
(ii) Labelling;
(iii) Change of particulars of a product;
(iv) Transfer of licenses;
(v) Manufacturing;
(vi) Storage including requirements as to containers;
(vii) Retailing;
(viii) Promotion of sale including product information;
(ix) Product recall;
(x) Product disposal;
(xi) The cost of product recall or product disposal;

(xii) Clinical trials; or

(xiii) Records and statistics pertaining to manufacture, sale, supply, import or export of any products

8. SUBMISSION OF APPLICATION

Application of product registration shall be submitted via the QUEST system at *https://quest3plus.bpfk.gov.my/front-end/login-chrome.php*. Refer to **5.3 How To Apply**.

Upon submission, the application shall be given a call number for reference, which is specific to a particular product. The applicant shall refer to this call number for all correspondence pertaining to the registration of the product.

9. SCREENING OF APPLICATION

After the product registration application has been submitted online, the application shall undergo an initial evaluation (screening process), which ensures that the submitted application is complete with the required data/ information. Further evaluation shall be done after payment for the application has been confirmed.

9.1 Satisfactory

Only a complete application shall be accepted and approved for payment. Upon screening approval, the applicant is requested to proceed with:

(i) payment:

The applicant is advised to keep a copy of the payment receipt as reference. A product reference number shall be given to the application upon payment confirmation.

Payment has to be made within thirty (30) days from the date of screening approval. The application form will be deleted from the system if payment has not been made within this stipulated time.

(ii) submission of hard copy documents (if applicable):

No.	Category of Product	Online Submission	Hard copy submission
1.	NDPs	All documents as required under Part I – IV	- Refer to *NCE Hardcopy Receiving Checklist* available in the NPRA website (*https://npra.gov.my/index.php/en/nce-application-forms*) - Further documentations may be requested as deemed necessary.
2.	Biologics	All documents as required under Part I – IV	- A CD containing complete dossier; - Hard copy of documents as required under Part I only; - Eight (8) hard copies of indexed folders containing proposed package insert, clinical overview and published clinical papers and/or in-house synopses; - Further documentations may be requested as deemed necessary.
3.	Generics (Scheduled Poison)	All documents	As requested e.g. big file size, unable to be submitted online
4.	Generics (Non-Scheduled Poison)	All documents	As requested e.g. big file size, unable to be submitted online
5.	Health Supplements	All documents	As requested e.g. big file size, unable to be submitted online
6.	Natural Products (Traditional and Homeopathic medicines)	All documents	As requested e.g. big file size, unable to be submitted online
7.	Natural Products with Therapeutic Claim	All documents as required under Part I – IV	- A copy of CD and a copy of documents as required under Part I – IV; - Further documentations may be requested as deemed necessary.

9.2 Non-Satisfactory

If the application is found incomplete during the screening process, the application shall be rejected and the applicant shall be notified via the system.

10. EVALUATION OF APPLICATION

10.1 Initiation of Review

Upon confirmation of payment, the application with the submitted data shall be evaluated. Review of applications shall follow a queue system. There shall be separate queues for the different categories of products and/ or according to the level of claims (e.g. general, medium or high claim for health supplements).

10.2 Correspondence

Correspondence via the system shall be sent to the applicant for any clarification or further supplementary data/ information or documentation pertaining to the application, if deemed necessary by the Authority.

The application shall be rejected if the applicant fails to respond to the correspondence from NPRA to submit the required clarification/ supplementary data/ information or documentation within six (6) months from the first correspondence date.

10.3 Evaluation Timeline for Product Registration

NO.	PRODUCT CATEGORY	* EVALUATION TIMELINE
(A)	**FULL EVALUATION**	
1.	New Drug Products (NCE)	245 working days
2.	New Drug Products (Hybrid)	210 working days
3.	Biologics	245 working days
4.	Generics (Scheduled Poison)	210 working days
5.	Generics (Non-Scheduled Poison)	210 working days
6.	Natural Products with Therapeutic Claim	245 working days
(B)	**ABRIDGED EVALUATION**	*** EVALUATION TIMELINE**
7.	Generics (Non-Scheduled Poison) a) Single active ingredient b) Two (2) or more active ingredients	a) 116 working days b) 136 working days
8.	Natural Products a) Single active ingredient b) Two (2) or more active ingredients	a) 116 working days b) 136 working days
9.	Health Supplements a) ** Single active ingredient b) ** Two (2) or more active ingredients ** *Applicable for:* *i) General or Nutritional Claims; and* *ii) Functional Claims (Medium Claims)* c) Disease Risk Reduction Claims (High Claims)	a) 116 working days b) 136 working days c) 245 working days

*Upon payment confirmation (Processing and Analysis Fee for Product Registration)

11. REGULATORY OUTCOME

11.1 Decisions of the Authority

A regulatory decision shall be made based on the outcome of the evaluation of the submitted documentation, and samples (if applicable). An application may be approved or rejected by the Authority, and the Authority's decision will be sent via email/ official letter to the PRH.

As stipulated under Regulation 11(1), CDCR 1984, , the Authority may, at any time reject, as well as cancel or suspend the registration of any product if there are deficiencies in safety, quality or efficacy of the product or failure to comply with conditions of registration.

Re-submission of product registration for a rejected application due to safety and efficacy reasons shall not be accepted within two (2) years after the rejection. However, if the product is registered in the reference countries, submission of application may be made earlier.

11.2 Product Registration Number

As stipulated under Regulation 8(8), CDCR 1984, upon registration of a product by the Authority, the PRH shall be notified by the Authority and a product registration number (i.e. MAL number) shall be assigned to the registered product via the QUEST system.

The registration number is specific for the product registered with the name, identity, composition, characteristics, origin (manufacturer) and PRH, as specified in the registration documents. It shall NOT be used for any other product.

The product registered with the registration number as stated in the Authority database shall have the name, composition, characteristics, specifications and origin as specified in the registration documents and Authority database.

Registration number appears as MALYYMM$$$$@##,

e.g. MAL11070001ACERS:

Alphabets/ symbols	Refers to:	
MAL	"Malaysia"	
YYMM	Refers to the year and month of registration by the Authority (e.g. 1107: July 2011)	
$$$$	Serial number for a registered product (e.g. 0001)	
@	Category of registered product i.e. A/ X/ N/ T/ H	
##	Refers to administrative code used by NPRA i.e. C/ E/ R/ S	
@ and ##	A	Scheduled Poison
	B	Natural Products with Therapeutic Claim
	X	Non-scheduled Poisons
	N	Health Supplements
	T	Natural Products (Traditional and Homeopathic Medicines)
	H	Veterinary Products
	C	Contract Manufactured (the product is manufactured by a GMP certified contract manufacturer)
	E	For Export Only (FEO) (the product is to be sold for export only and not for sale in the local market)
	R	Packed and/or repacked (the product is packed and/or repacked by an approved GMP certified packer and/or repacker)
	S	Second source (the product is from a second source/ approved second manufacturer)
	Z	Products gazetted as zero-rated under the Goods and Services Tax Act 2014, Goods and Services Tax (Zero-Rated Supplies) Order 2014

11.3 Certificate of Registration

Form 1 (Certificate of Registration) for a product with the provisions, conditions, limitations and etc. of the registration, as stipulated under Regulation 8(8) of CDCR 1984, has been deleted from the regulation in 2006 via amendment of PU(A) 336/06. Therefore, the certificate will no longer be issued by the Authority.

Reference:
Bil. (100)dlm.BPFK/PPP/01/03 Jld. 2. *Pemansuhan Pengeluaran Sijil Perakuan Pendaftaran (SPP)* (21 January 2013)

The applicant shall refer to the product registration approval notification sent by the Authority or the **Approved Product Registration List** in the NPRA website.

The registration status of a product shall be valid for five (5) years or such period as specified in the Authority database (unless the registration is suspended or cancelled by the Authority).

Upon approval for product registration by the Authority, the applicant shall fulfill all commitments and conditions imposed with approval of the product registration and shall be responsible for the maintenance of the product in terms of quality, safety and efficacy throughout the validity period of registration. Failure to do so may result in rejection of future application for renewal of the product registration.

The applicant shall notify the Authority of any changes to the product's efficacy, quality and safety, as described in **Section E: Post-Registration Process.**

11.4 Appeal Towards Decision of the Authority

Refer to **Appendix 24: Appeal.**

SECTION C: QUALITY CONTROL

The requirement for the submission of the protocol of analysis (POA), analytical method validation (AMV) and product samples for laboratory testing are presented in this section.

The POA and AMV shall be submitted to the Centre of Product & Cosmetic Evaluation (PPPK) via the online QUEST system.

Documents to be submitted via online QUEST system for finished product:

1. E12 : Complete POA for finished product including preservatives and diluents (if any).
2. E13 : (a) Complete testing methods and results for AMV with all relevant validation parameters, including acceptance criteria and supporting raw data (e.g. chromatograms, spectrums, etc.)
   (b) Summary of AMV which includes all relevant validation characteristics, its acceptance criteria and results.

Documents to be submitted via online QUEST system for Active Pharmaceutical Ingredient, API:

1. S 4.2 : Complete POA for drug substance(s)
2. S 4.3 : Complete testing methods and results for AMV for drug substance(s) with all relevant validation parameters, including acceptance criteria and supporting raw data (e.g. chromatograms, spectrums, etc.)

12. GUIDELINE FOR THE SUBMISSION OF PROTOCOL OF ANALYSIS (POA)

This guideline consists of general and specific requirements for POA submission. The general requirements are referred to POA content whilst details of the test methods are illustrated in the specific requirements.

Refer to **Appendix 25: Guideline for the Submission of Protocol of Analysis (POA)**.

13. GUIDELINE FOR THE SUBMISSION OF ANALYTICAL METHOD VALIDATION (AMV) DOCUMENTS

Refer to **Appendix 26: Guideline for the Submission of Analytical Method Validation (AMV) Documents**.

14. GUIDELINE FOR THE SUBMISSION OF PRODUCT SAMPLES FOR LABORATORY TESTING

14.1 Natural Products

a) In accordance with Directive No. 8, 2020, *BPFK/PPP/07/25 (8) Jld.4*. *Direktif Penerimaan Keputusan Pengujian Pra-Pendaftaran Produk Semulajadi dari Makmal Swasta yang Telah Diiktiraf oleh Bahagian Regulatori Farmasi Negara (NPRA) dan Makmal Kawalan Kualiti Pengilang Tempatan*, starting from 1 December 2020, the applicant is no longer required to submit samples of natural product for laboratory testing to NPRA.

b) The PRH shall submit a Certificate of Analysis (CoA) for the purpose of product registration evaluation.

c) For further details regarding submission of the CoA, refer to **Appendix 7: Guideline on Registration of Natural Products, 2.7.7 Certificate of Analysis (Finished Product)**.

14.2 Pharmaceutical Products *(Upon NPRA request)*

a) Sample shall be submitted with a cover letter containing the following information:
   (i) Name and reference number of the product;
   (ii) Name and address of PRH;
   (iii) Name, email address and contact number of authorized person

b) Samples submitted must be in their original packaging and labelling.

c) Samples submitted must be from the same manufacturing premise as stated in the application for registration.

d) Samples submitted must have an expiry date of least one (1) year from the date of submission and must be from the same batch.

e) An official CoA and the recent shelf-life specification from the manufacturer for the same batch of sample must be submitted with the sample.

f) The quantity of samples submitted must match the quantity requested.

g) Other materials such as HPLC columns, reagents, etc. must be submitted when requested.

h) Reference standards are required to be submitted along with the pharmaceutical products. Requirements for these reference standards are as follows:

(i) The type and quantity of reference standards submitted must match the type and quantity requested;

(ii) Reference standards submitted must have an expiry date of least one (1) year from the date of submission. In special situations, an expiry date of not less than six (6) months may be accepted;

(iii) All reference standards must be submitted with an official CoA for the same batch with the stated purity (as is, dried, anhydrous etc.) and all other relevant information (water content, loss on drying etc.);

(iv) All reference standards must be properly labelled with the name, batch number, purity and expiry date;

(v) All reference standards must be submitted in small, sealed air-tight amber glass containers.

i) The Centre of Compliance & Quality Control (PKKK) shall issue import permit for pharmaceutical products. The applicant shall ensure that the import permit is endorsed by the enforcement officer at the entry point.

SECTION D: INSPECTION, LICENSING, CERTIFICATE

Inspection and licensing of manufacturing premises or facilities, importers and wholesalers of registered products or notified cosmetics on the basis of compliance with Good Manufacturing Practice (GMP) and Good Distribution Practice (GDP) are vital elements of drug control. Compliance with GMP and GDP are prerequisites for the application of a manufacturing license as well as product registration or cosmetic notification, whereas compliance with GDP is a prerequisite for the application of a wholesale license or import license.

15. INSPECTION

Inspection of GMP and GDP are conducted to ensure the compliance of manufacturers, importers and wholesalers with current GMP and GDP requirements besides ensuring that registered products and notified cosmetics in the market are safe, efficacious and of quality. Refer to **Appendix 27: Inspection**.

16. LICENSING

According to the Regulation 12, CDCR 1984, any company that wants to manufacture, import or wholesale any registered products needs to have a valid Manufacturer's License, Import License or Wholesaler's License. Refer to **Appendix 28: Licensing**.

17. CERTIFICATE

Refer to **Appendix 29: Certificate** for information regarding:

- Certificate of Pharmaceutical Product (CPP)
- Good Manufacturing Practice (GMP) Certificate

SECTION E: POST-REGISTRATION PROCESS

18. MAINTENANCE OF REGISTRATION

a) The registration of a product shall be valid for **five (5) years** or such period as specified in the Authority database (unless the registration is suspended or cancelled by the Authority).

b) Application for product re-registration (renewal of product registration) shall be submitted **within six (6) months prior to the expiry** of the validity period of a product registration with the appropriate fee. A letter of reminder for product re-registration shall be issued to the product registration holder three (3) months prior to the expiry date of a product registration.

c) After the expiry date, the status of product registration shall be automatically changed to "expired", following which the applicant will not be able to submit an application for product re-registration. Any form of appeal shall not be considered if the re-registration application is not submitted before the expiry date of a product registration since the reminder letter is issued three (3) months prior to the expiry date. A new registration application is required if the applicant wishes to continue to market the product.

d) After the expiry date of the product registration, the product is deemed unregistered. For products with their re-registration on hold due to unmet requirements past their registration expiry date, the new registration date shall be updated according to the DCA meeting date when the re-registration application is approved by the DCA.

e) The application for product re-registration shall only be submitted when all registration requirements have been complied with. Failure to do so shall result in the re-registration application being rejected by the Authority.

f) The application for product re-registration shall be submitted with proof of payment via the online QUEST system.

g) The non-refundable processing fees for product re-registration are:

(i)	Traditional product	: RM 500.00 per product
(ii)	Pharmaceutical product (including Health Supplement)	: RM1,000.00 per product

h) The following are requirements for product re-registration of different product categories, where applicable:

(i) Exemption of bioequivalence study report for all registered generic products in immediate release, oral, solid dosage form (starting 15 March 2020).

Reference:
Bil. (2) dlm. BPFK/PPP/07/25 Jld. 4
Arahan Pengarah Kanan Perkhidmatan Farmasi Bil. 2 Tahun 2020: Direktif Pertimbangan Pengecualian Keperluan Data Bioekuivalens (BE) Bagi Produk Generik Dalam Bentuk Oral Solid, Immediate Release *Yang Mengemukakan Permohonan Pendaftaran Semula* (10 March 2020)

(ii) Products previously registered as "Pendaftaran Hak" or "Not Commercially Viable Medicine (NCVM)".

Reference:
Bil. (20) dlm. BPFK/PPP/07/25 Jld. 2
Arahan Pengarah Kanan Perkhidmatan Farmasi Bil. 20 Tahun 2018: Direktif Permohonan Pendaftaran Semula Produk Yang Pernah Didaftarkan secara "Pendaftaran Hak" dan Produk "Not Commercially Viable Medicine (NCVM)" (26 June 2018)

(iii) Patient dispensing pack size for pharmaceutical product containing scheduled poison or non-scheduled poison with tablet/ capsule dosage form, including oral liquid preparation and dermatological preparation.
Refer to **Appendix 23: Patient Dispensing Pack for Pharmaceutical Products.**

(iv) Bioequivalence study report for all registered generic products containing scheduled poison with immediate release, oral, solid dosage form (starting 1 January 2013)

Reference:
Bil. (10) dlm. BPFK/PPP/01/03 Jld.1
Arahan Pengarah Kanan Perkhidmatan Farmasi Bil. 1 Tahun 2011: Direktif Penguatkuasaan Keperluan Kajian Bioekuivalens Bagi Semua Produk Generik "Immediate Release, Oral, Solid Dosage Form" *Yang Mengandungi Bahan Aktif Racun Berjadual Serta Akreditasi Pusat Kajian Bioekuivalens* (2 March 2011)

(v) Bioequivalence study report for all registered generic products containing scheduled poison with effervescent, dispersible, orodispersible, sublingual, buccal and chewable dosage form (For expiring product registrations starting 1 January 2019)

References:
Bil. (27) dlm. BPFK/PPP/07/25
Arahan Pengarah Kanan Perkhidmatan Farmasi Bil. 3 Tahun 2015: Direktif Penguatkuasaan Keperluan Kajian Bioekuivalens (BE) Bagi Produk Generik Dalam Bentuk Dos Oral Tablet/Kapsul Yang Bersifat Effervercent, Dispersible, Orodispersible, Sublingual, Buccal *Dan* Chewable *Yang Mengandungi Bahan Aktif Racun Berjadual* (23 February 2015)

Bil. (45) dlm.BPFK/PPP/01/03 Jld.3
Lanjutan Tarikh Penguatkuasaan Untuk Memenuhi Keperluan Kajian Bioekuivalens (BE) Bagi Produk Generik Dalam Bentuk Dos Oral Tablet/Kapsul Yang Bersifat Effervescent, Dispersible, Orodispersible, Sublingual, Buccal *dan* Chewable *Yang Mengandungi Bahan Aktif Racun Berjadual* (31 May 2016)

(vi) Regulatory control of active pharmaceutical ingredient (API) for all dosage form of registered pharmaceutical products containing scheduled poison (For expiring product registrations starting from 1 January 2020)

- API information shall be submitted at least one year prior to the product registration expiry date.
- Refer to **Appendix 11: Regulatory Control of Active Pharmaceutical Ingredients**.

References:

Bil. (7) dlm.BPFK/PPP/07/25
Arahan Pengarah Kanan Perkhidmatan Farmasi Bil. 8 Tahun 2013: Direktif Pelaksanaan Pengawalan Bahan Aktif Farmaseutikal Bagi Produk Generik (Fasa II) (16 January 2014)

Bil. (11) dlm.BPFK/PPP/01/03 Jld.3
Lanjutan Tarikh Pelaksanaan Pengawalan Bahan Aktif Farmaseutikal (API) Bagi Produk Farmaseutikal Berdaftar Yang Mengandungi Racun Berjadual (27 June 2014)

(vii) For pharmaceutical products submitted for registration before 2009, applicants shall ensure that the Zone IVB stability study for the products have been conducted and granted variation approval before submission of re-registration application.

References:

Bil. (1) dlm. BPFK/PPP/01/03 Jld.3
Keperluan Data Kajian Stabiliti Dalam Zon IVb Bagi Produk Farmaseutikal Berdaftar (5 April 2013)

Bil. (5) dlm. BPFK/PPP/01/03 Jilid 3
Lanjutan Tarikh Kuatkuasa Untuk Memenuhi Keperluan Data Kajian Stabiliti Dalam Zon IVb Bagi Produk Farmaseutikal Berdaftar (14 August 2013)

For pharmaceutical products requiring exemption from Zone IVb requirements, applicants shall submit the exemption request via variation application (MiV-PA) through the online QUEST system.

(viii) Valid GMP document/ certificate for imported product (starting 1 January 2014)

To maintain the registration of an imported product, the PRH shall comply with GMP requirements as stated in the directive issued by the Director of Pharmaceutical Services under Regulation 29, CDCR 1984.

Refer to Guidance Document for Foreign GMP Inspection

References:

Bil. (25) dlm BPFK/PPP/01/03 Jld.1
Arahan Pengarah Kanan Perkhidmatan Farmasi Bil. 1 Tahun 2012: Direktif Mengenai Syarat Pendaftaran Produk Farmaseutikal Dari Luar Negara Berkaitan Keperluan Amalan Perkilangan Baik (APB) (9 February 2012)

Bil. (96) dlm.BPFK/PPP/01/03 Jld.2
Surat Pekeliling Bagi Direktif Mengenai Syarat Pendaftaran Produk Farmaseutikal Dari Luar Negara Berkaitan Keperluan Amalan Perkilangan Baik (APB) (28 December 2012)

Bil. (32) dlm. BPFK/PPP/07/25
Arahan Pengarah Kanan Perkhidmatan Farmasi Bil. 1 Tahun 2016: Direktif Mengenai Keperluan Pemeriksaan Amalan Perkilangan Baik (APB) Luar Negara Bagi Tujuan Pendaftaran/ Pendaftaran Semula Produk Farmaseutikal Berdaftar Dengan Pihak Berkuasa Kawalan Dadah (PBKD) (22 January 2016)

Bil. (42) dlm.BPFK/PPP/07/25
Arahan Pengarah Kanan Perkhidmatan Farmasi Bil. 11 Tahun 2016: Direktif Mengenai Penerimaan Pengesahan Pematuhan Amalan Perkilangan Baik (APB) Bagi Tujuan Pendaftaran Semula Produk Farmaseutikal Berdaftar dengan Pihak Berkuasa Kawalan Dadah (PBKD) (30 June 2016)

Bil. (15) dlm. BPFK/PPP/06/06 Jld.47
Pendaftaran Bersyarat Bagi Produk-Produk Dengan Sijil Amalan Perkilangan Baik (APB) dari Ministry of Economic Affairs, Taiwan (1 February 2017)

KKM/NPRA.PKP/600-2/11(7)
Arahan Pengarah Kanan Perkhidmatan Farmasi Bil. 4 Tahun 2018: Direktif Mengenai Penerimaan Pengesahan Pematuhan Amalan Perkilangan Baik (APB) Bagi Pengilang Farmaseutikal Bagi Tujuan Pendaftaran Baru/ Pendaftaran Semula Produk Farmaseutikal Berdaftar Dengan Pihak Berkuasa Kawalan Dadah (PBKD) (16 May 2018)

(ix) Amendment of product name consisting of only generic name for registered pharmaceutical product containing scheduled poison and non-scheduled poison (starting 1 January 2017)

Reference:
Bil. (39) dlm. BPFK/PPP/01/03 Jld.3
Pekeliling Penggunaan Nama Generik Pada Nama Produk Bagi Produk Farmaseutikal (21 December 2015)

(x) Endorsement letter of ancillary medical device component (from Medical Device Authority, Malaysia) for re-registration of drug-medical device combination product (For expiring product registrations starting from 1 July 2019)

Note: Also refer to Guideline for Registration of Drug-Medical Device and Medical-Device-Drug Combination Products.

Reference:
Bil. (9) dlm. BPFK/PPP/07/25 Jld.1
Arahan Pengarah Kanan Perkhidmatan Farmasi Bil. 4 Tahun 2017: Direktif Kuatkuasa Pemakaian Guideline for Registration of Drug-Medical Device and Medical Device-Drug Combination Products (10 March 2017)

i) Products manufactured and sold or supplied by the PRH before the product registration expiry date or cancellation date, do not require to be recalled from the market and may be sold until end of product shelf life. However, products with quality, safety and/or efficacy issues shall be recalled immediately from the market upon the product registration expiry date or cancellation date or at any other time stipulated by NPRA.

j) The PRH shall submit a written request to the DCA Secretary to deplete any existing unsold stocks after the product registration expiry date or cancellation date. If approval is granted, the PRH shall be held responsible for the batches and quantity requested in the event of any pharmacovigilance issues or quality defects associated with those product batches sold after the product registration expiry date or cancellation date.

19. WITHDRAWAL OF PRODUCT REGISTRATION

a) The PRH shall submit an official written request to the DCA Secretary if they decide to withdraw the registration of a product before the end of the validity of such registration. The PRH is required to state the reasons for the withdrawal decision in their request. The PRH is also required to inform their manufacturer/ contract manufacturer of their withdrawal decision.

b) The registration of a product, once withdrawn, shall not be reinstated. A new application for product registration is required if the PRH wishes to have the product registered again at a later date.

c) Products manufactured and sold or supplied by the PRH before the registration termination date, do not require to be recalled from the market and may be sold until end of product shelf life. However, products with quality, safety and/or efficacy issues shall be recalled immediately from the market upon the product registration termination date or at any other time stipulated by NPRA.

d) The PRH shall submit a written request to the DCA Secretary to deplete any existing unsold stocks after the registration termination date. If approval is granted, the PRH shall be held responsible for the batches and quantity requested in the event of any pharmacovigilance issues or quality defects associated with those product batches sold after the registration termination date.

20. AMENDMENTS TO PARTICULARS OF A REGISTERED PRODUCT

Throughout the life cycle of a registered product, changes to improve product efficacy, quality and safety are likely to occur. Therefore, the applicant shall inform the Authority of any changes or amendments made to particulars of a registered product.

20.1 Variation

a) Variation refers to the change of particulars of a registered product. No change of any particulars of a registered product [except for Minor Variation Notification (MiV-N)] shall be made without prior approval from NPRA.

b) All supporting documents shall be submitted in accordance with the specified conditions for each type of variation.

c) Variation applications and processing fees shall be made according to specific product categories in the Malaysian Variation Guideline (MVG).

d) If deemed necessary, NPRA reserves the right to request for additional supporting documents and variation approval letters from other regulatory bodies for all product categories.

e) The registration of a product shall be reviewed for suspension or cancellation if changes that fall under Major Variation (MaV) and Minor Variation Prior Approval (MiV-PA) are implemented without prior approval of the Authority.

f) Variation application shall be submitted through the online QUEST system.

20.1.1 Variation Application for Pharmaceutical Products

Variation application for pharmaceutical products shall be done according to the Malaysian Variation Guideline (MVG).

Reference: *Bil. (2) dlm. BPFK/PPP/07/25*, *Arahan Pengarah Kanan Perkhidmatan Farmasi Bil. 3 Tahun 2013: Direktif Untuk Melaksanakan* Malaysian Variation Guideline (MVG) (29 April 2013)

For unregulated drug substance: **Appendix 30: Conditions and Supporting Documents Required for an Application of Variation** are still applicable for application for variations and supporting documents related to drug substance until further notice.

20.1.2 Variation Application for Health Supplement and Natural Products

Variation application for Health Supplement Products and Natural Products shall be done according to the Malaysian Variation Guideline (MVG) for Natural (Traditional Medicine & Homeopathy) and Health Supplement Products (Abridged Evaluation).

Reference: Directive No. 14, 2016. *BPFK/PPP/07/25(45)*: *Direktif Untuk Melaksanakan* Malaysian Variation Guideline (MVG) for Natural (Traditional Medicine & Homeopathy) and Health Supplement Products (Abridged Evaluation) (26 July 2016)

20.1.3 Variation Application for Biological Products

Variation application for biologics shall be done according to the Malaysian Variation Guidelines for Biologics (MVGB).

Reference: Directive No. 2, 2017. *BPFK/PPP/07/25(7)Jld.1*: *Direktif Untuk Melaksanakan* Malaysian Variation Guideline for Biologics (MVGB) (15 February 2017)

20.2 Change of Manufacturing Site (COS)

Refer to **Appendix 31: Change of Manufacturing Site (COS)**.

20.3 Change of Product Registration Holder

This refers to a transfer of marketing authorization from the existing PRH to another proposed new holder. This change application allows for the same registration number of the registered product to be maintained. Refer to **Appendix 32: Change of Product Registration Holder**.

20.4 New/ Additional Indication

New/ additional indication is defined as an indication not initially approved for a registered pharmaceutical product. This may include new therapeutic indication or indication for new age group, such as usage in children. This does not include changing/ rephrasing of sentences.

Two (2) types of evaluation processes are available for a new/ additional indication application:

a) Full Evaluation Process

This applies to a new indication that has been registered in any one (1) of the eight (8) DCA's reference countries (United Kingdom, Sweden, France, United States of America, Australia, Canada, Japan and Switzerland).

This application will require comments from relevant specialists.

b) Verification Process

This applies to a new indication that has been registered in any two (2) DCA's reference countries (United Kingdom, Sweden, France, United States of America, Australia, Canada, Japan, Switzerland and EMA).

Note:
The proposed new indication shall be the same as the approved new indication in the reference countries.

An application to add a new indication deemed not feasible for submission to DCA's reference agencies may be considered for evaluation by NPRA on a case-by-case basis.

Other supporting documents deemed necessary shall be submitted upon request to support the efficacy and safety of the proposed additional indication.

The supporting documents may include but are not limited to the following:

a) Approval of Additional Indication(s) in country of origin;
b) Approval status in reference countries, its corresponding approval letter and approved Package Insert;
c) Approval Indication status in ASEAN Member States and its approved corresponding package insert;
d) Revised Package Insert;
e) World Wide Approval status;
f) Consumer Medication Information Leaflet (RiMUP);
g) Clinical Expert Reports;
h) Synopsis of Individual Studies;
i) Clinical Studies Report/ In-House Clinical Trials;
j) Published Clinical Papers;
k) Current Periodic Benefit-Risk Evaluation Report (PBRER)

20.5 Convenient Pack

a) Convenient pack refers to registered products packed together in a single packaging unit for consumers, such as a confinement set or *set jamu bersalin*.

b) Individually registered products are allowed to be packed together and marketed as a convenient pack, provided that the application is justified satisfactorily.

c) The convenient pack is applicable for registered products in the category of;
   (i) Health supplements
   (ii) Natural products
   Or registered products from both categories (i) and (ii)
   (iii) Non-Scheduled Poison (OTC)
   (Only between OTC products with Abridged Evaluation category)

d) Individually registered products in the convenient pack can be sold individually or as a pack.

e) Conditions for application:
   (i) Individually registered products proposed to be packed together as a convenient pack shall be sourced from the same product owner/ PRH.
   (ii) Submission of the application shall be made by the same PRH.
   (iii) The manufacturing site for the convenient pack shall be a GMP certified facility.
   (iv) Application shall be made via variation application.
   (v) The PRH is required to submit the convenient pack label and the individual labels via application for variation under Part D2 (outer label).
   (vi) The convenient pack label shall contain the same information as in the primary label.
   (vii) Approved indication of each individually registered product in the convenient pack remains unchanged. There shall be no common specific indication for the convenient pack.

f) Labelling requirement specific for the convenient pack:

Outer Label	Immediate Label
Contents in the labelling of each individually registered product have to be included in the outer label of the convenient pack.	As per labelling requirements for registered products.

Note:
For the purpose of application submission: If the individually registered products are also marketed independently, both the outer label of the packaging sold independently and the outer label of the convenient pack are required to be submitted.

g) **The differences in a Convenient Pack from a Combination Pack (Combo Pack) and Starter Pack/ Patient Initiation Pack/ Dose Adjustment Pack are as follows**:

No.	Particulars	Convenient Pack	Combination Pack (Combo Pack)	Starter Pack/ Patient Initiation Pack/ Dose Adjustment Pack
1.	New registration number (MAL No.) to be assigned upon approval	No	Yes	No
2.	Mode of application	Variation	Application for registration as a new product	Application for registration as a new product and variation
3.	Purpose of product	For convenience of the consumer	For therapeutic regimen	For dosing regimen
4.	New indication	No	Yes	No
5.	Sale of product	Can be sold individually or as a pack	Only to be sold as a pack	Only to be sold as a pack
6.	Example	Confinement Set or *Set Jamu Bersalin*	Klacid HP7 (for treatment of peptic ulcer diseases associated with H. pylori infection)	Products that require dose tapering either to reduce systemic side effect or for dose adjustment to achieve the desired maintenance dose

21. POST-MARKETING ACTIVITIES

21.1 Pharmacovigilance

Reporting Adverse Drug Reaction (ADR) and Adverse Events Following Immunisation (AEFI) and Safety Updates

a) In accordance with Regulation 28, CDCR 1984, the PRH or any person who possesses any registered product shall inform immediately the Director of Pharmaceutical Services of any adverse reaction arising from the use of the registered product.

b) All PRH must ensure that the company has a pharmacovigilance system is in place and takes appropriate action, when necessary.

c) PRHs are required to monitor and report any product safety issues that arises locally or internationally to the NPRA and comply with all safety-related directives issued by the Authority.

d) The product registration status may be affected if the PRH fails to inform the Authority of any serious adverse reactions upon receipt of such reports.

e) The WHO encourages reporting of ALL ADR and AEFI.

f) For further information, refer to the Malaysian Guidelines on Good Pharmacovigilance Practices (GVP) for Product Registration Holders, First Edition, August 2021.

21.2 Post-Market Surveillance

It is the prime responsibility of the PRH to ensure that products marketed are in accordance with the standards and requirements of the Authority.

Registered products may be sampled and tested for compliance with official or pharmacopoeial standards or specifications agreed by the manufacturer. Labels and package inserts of the samples may also be checked to ensure compliance with the requirements approved.

The Authority shall take necessary action on products that do not conform to the standards/ specifications and requirements in the form of warnings or recalls.

The PRH has up to thirty (30) days to identify the cause of defect and actions to be taken for improvement.

Product Complaints

a) The PRH shall notify NPRA of any product quality related problems (with registered products) of which the PRH is aware.

b) It is also the responsibility of the prescribers, pharmacists, as well as all other health professionals who come into contact with the drug to report any product complaints to NPRA by using the NPRA complaint form i.e. BPFK 419/ BPFK 418 with complaint sample (if any).

c) All complaints received shall be investigated by NPRA as well as the PRH/ manufacturer. It is the responsibility of the company to determine the appropriate corrective and preventive action.

Reference: Chapter 6, Guidelines on Good Distribution Practice, Third Edition, 1 January 2018.

Product Recalls

a) The decision for recall of a product shall be made when there is actual or potential risk to the product users. Recalls may be done voluntarily by the PRH or as directed by the Director of Pharmaceutical Services Division, Ministry of Health Malaysia;

b) The PRH is responsible for conducting recalls of defective or unsafe products. No recall shall take place without first consulting/ informing the Authority.

Reference: Chapter 7, Guidelines On Good Distribution Practice, Third Edition, 1 January 2018.

21.3 Punitive Action by the Authority

Adulteration

Punitive action shall be taken against companies who are involved in adulteration.

For any registered products found to have been adulterated, the following action shall be taken by the Authority:

a) The registration of the related product shall be cancelled and recall of all batches of the product shall be done immediately;

b) The manufacturer's license of the related manufacturer shall be revoked for six (6) months for the first offence and one (1) year for the subsequent offence, from the date of the revocation letter from the Authority;

c) All transactions (including application for product registration, application for change of PRH, application for change of manufacturing site) for the adulterated PRH shall be frozen for six (6) months for the first offence and one (1) year for the subsequent offence, from the date of the cancellation letter from the Authority.

Reference: *Bil. (30) dlm.BPFK/PPP/01/03*, *Tindakan Punitif Ke Atas Syarikat Yang Terlibat Dengan Kes Produk Campur Palsu* (13 May 2009)

21.4 Notification of Product Quality Issue

NPRA may notify other regulatory authority or stakeholder relating to the recall and/or other regulatory action of a defective medicinal product in order to protect public health.

APPENDIX 1

FOOD - DRUG INTERPHASE (FDI) PRODUCTS

This guide serves to assist in determining if a product is regulated by the National Pharmaceutical Regulatory Agency (NPRA) or by the Food Safety and Quality Division (FSQD) of the Ministry of Health Malaysia.

1. INTRODUCTION

Malaysians are now more health conscious and there is generally greater awareness of the importance of nutrition to overall well-being. In recent years, many consumers also rely on a variety of "dietary supplements" to improve their health. These diverse products are freely available through a myriad of outlets. A variety of products are available in the market, supposedly for the maintenance, prevention and even treatment of chronic diseases. These products may range from foods modified to have special properties or pure forms of vitamins and minerals to extracts of various botanical or animal products.

It is important to monitor and regulate the marketing and sale of these products to protect the interest and health of the consumer. Some of these products are not clearly defined as "food" or "drugs" but are freely marketed. Such products include a variety of so-called health products and have been termed as "food-drug interphase (FDI) products".

In order to better define and regulate the FDI products, both the NPRA and the FSQD, Ministry of Health Malaysia formed the Committee for the Classification of Food-Drug Interphase Products in 2000. The main Terms of Reference of the Committee is to assist both Divisions in classifying, in a consistent manner, any application from the industry not clearly defined either as a food or drug product. The Committee also serves as a platform in strengthening and updating the relevant regulations as well as to provide scientific input on these products.

2. FOOD PRODUCTS REGULATED BY FSQD INCLUDE:

2.1 100% food ingredients

2.2 Food products with or without active ingredients (e.g.: herbs, vitamins, minerals, etc.) such as:

i) Instant drink products containing sugar and creamer (e.g. premix coffee, tea, chocolate, soy, cereal)

ii) Meat essence products (liquid) (e.g. chicken essence, ostrich essence, duck essence, fish essence, etc.)

iii) Ready to drink products (beverages) without dosing instruction in cheer packs/ cans / packet drinks.

iv) Cordial products with recommended dilution ratio (e.g. dates cordial, grape cordial)

v) Vinegar products (powder & liquid) (e.g. apple vinegar, dates vinegar, etc.)

vi) Honey products (powder & liquid)

2.3 Isotonic drink products, sport nutrition products and special purpose food products

2.4 Products in conventional food form, e.g. biscuit, cake, confectionery, candy/sweet, gummy, noodle

2.5 Products used for cooking and food preparation (e.g. cooking oil (olive oil, coconut oil, sunflower oil), herbs and spices)

2.6 Herbs and spices in crude form without medicinal/ health claim

3. PRODUCTS REGULATED BY NPRA INCLUDE:

3.1 Products containing active ingredient(s) with or without excipient

3.2 Products containing specific active ingredients, which possess high pharmacological or therapeutic potencies. Examples of the ingredients are paracetamol, glucosamine, tranexamic acid, aspirin, and substances listed in Poisons Act 1952

3.3 Products containing specific active ingredients, which possess dose-related therapeutic potencies such as:

- Plant sterols/ stanols and esters that are consumed ≥ 3.5g/day
- Psyllium husk that are consumed ≥ 3.5g/day
- Products containing senna ≥ 0.5g

3.4 Products in pharmaceutical dosage form, such as soft gel, capsule or tablet (that is to be directly swallowed), sublingual, buccal, spray into the mouth, etc.

4. FDI PRODUCTS

Generally, FDI products are products with combination of food ingredients and active ingredients for oral consumption. FDI products are not clearly defined as food or drug. Examples of food ingredients are fruits, vegetables, meat, poultry, milk, cocoa and cereal. Examples of active ingredients are vitamins, minerals, herbs, enzymes, probiotics, prebiotics, amino acids, peptides, coral calcium, fatty acids, collagen, chia seed, astaxanthin, lutein and other ingredients that are not traditionally consumed as food. FDI products may be presented in the form of powder, liquid, semisolid forms such as gel/ jelly, chewable tablet, drops, granule, etc.

4.1 Classification of FDI Products

FDI is **not a product category** and it is important to determine whether the products are regulated as drug (under the NPRA's purview), or as food (under the FSQD's purview) because different regulatory requirements apply. The classification of FDI products are based on criteria, as outlined below:

a) Main criteria

i. Negative List for FDI as listed in Table I: Negative List For FDI:

FDI products containing ingredient(s) from Negative List for FDI shall be regulated by NPRA; or

ii. Medicinal/ health claim refer to the term "medicinal purpose" as stipulated in the Sales of Drug Act 1952, Section 2:

FDI products not containing ingredient(s) from Negative List for FDI and with medicinal/ health claim shall be regulated by NPRA; or

FDI products not containing ingredient(s) from Negative List for FDI and without medicinal/ health claim shall be regulated by FSQD.

iii. Products intended to be used or capable, or purported or claimed to be capable for a medicinal purpose (e.g. products used for the health benefit of eyes, body weight control, gastrointestine, brain, etc.) shall be regulated by NPRA.

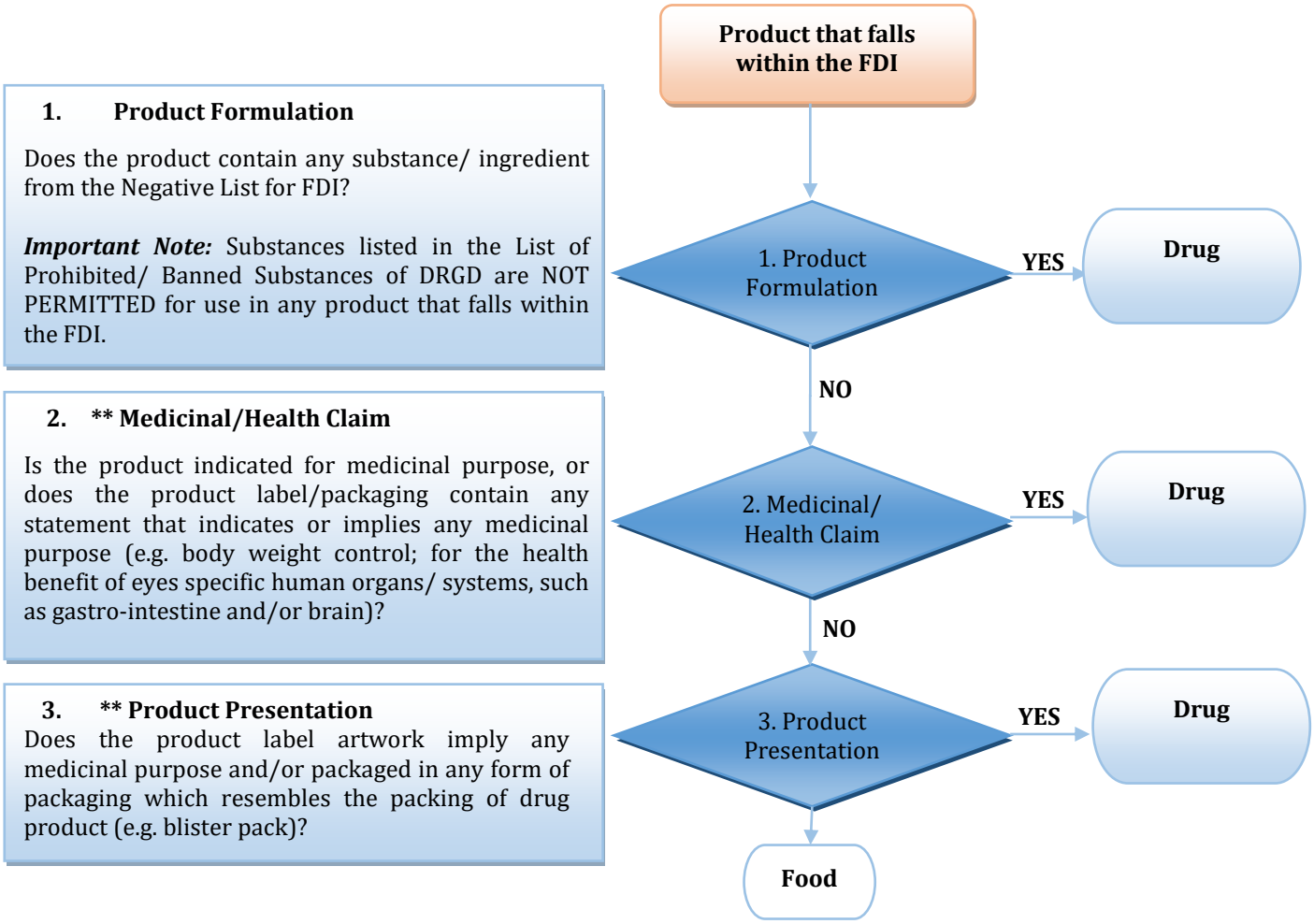
b) Other criteria

When there is greater uncertainty regarding the safety of a FDI product, such product shall be regulated by NPRA. This is to enable closer monitoring of such product to safeguard the health of the consumer.

Reference: *Pekeliling Kriteria Baru Pengkelasan Produk Food-Drug Interphase (FDI)* (7 August 2014) *Bil. (19)dlm.BPFK/PPP/01/03 Jld.3*

CLASSIFICATION FLOWCHART OF FDI UNDER FOOD OR DRUG

- The following flowchart serves only as a guide to help determine the category of the product that falls within the FDI.
- Contact the relevant regulatory agencies for clarification, or seek classification service from NPRA by submitting a classification application should there be doubt or uncertainty pertaining to the category of the product.
- Read the governing legislations and other regulatory requirements and guidelines that apply to the product before using this guide.



Note: ** NPRA reserves the right to use its discretion to make decision if any issue of subjectivity arises.

5. ADDITIONAL NOTES

5.1 Substances listed in the prohibited/ banned ingredient list of the Drug Registration Guidance Document (DRGD) and Schedule Poison shall not be permitted for use in any FDI products.

5.2 Products categorized as a natural product are not allowed to contain creamer.

5.3 Food products are not allowed to be packed in blister pack/ any other form of packaging that resembles the packaging of drug product.

5.4 Any foods or combination of foods that are regulated by FSQD shall not be in pharmaceutical dosage form. Such products are advised to be reformulated into a non-pharmaceutical dosage form.

5.5 Products containing only ingredient(s) such as roselle, jasmine, rose, chamomile, chrysanthemum flower, ginger (rhizome), vanilla(stem), mint leaf, lemon peel and cinnamon bark (with/without C*amelia sinensis*) will be regulated by FSQD.

5.6 Fruit ingredients that are not commonly consumed as food in Malaysia will be considered as active ingredient.

Table I: Negative List for FDI

No.	Ingredient	Common / Other name
1	***Actaea racemosa***	Black Cohosh, Cimicifuga racemosa
2	***Antiaris toxicaria (Pers.) Lesch.***	Bark cloth tree, antiaris, false iroko, false mvule, upas tree
3	***Artemisia Spp. (all species)***	Wormwood, Mugwort
4	***Aspidosperma Quebracho-Blanco Schltdl***	Kebrako, White Quebracho
5	***Atropa Spp. (all species)***	Antropa belladonna (deadly nightshade)
6	***Azadirachta indica***	Nimba, Neem
7	**Bile**	
8	***Brucea javanica, Brucea amarissima***	Sumatrana amarissimus, Java brucea
9	***Bufo gargarizans Cantor, Bufo melanostictus Schneider, Bufo vulgaris Lour***	Toad, Samsu, kodok, kerok
10	***Calotropis Spp. (all species)***	Apple of Sodom, Crown flower
11	***Cannabis Spp. (all species)***	Marijuana, Hemp
12	***Catharanthus Spp. (all species)***	Periwinkle
13	***Chelidonium majus***	Celandine, Great Celandine, Nipplewort
14	***Chondodendron Spp. (all species)***	
15	***Claviceps Spp. (all species)***	Ergot
16	***Colchicum Spp. (all species)***	Autumn crocus, Meadow saffron, Naked lady
17	***Conium maculatum***	Hemlock
18	***Coptis chinensis, Coptis teeta***	Chinese Goldthread
19	***Croton tiglium L.***	Croton
20	***Datura Spp. (all species)***	Jimson weed, Devil's apple, Green Dragon, Zombie's Cucumber, Moon Weed, Trumpet Lily, Stinkweed
21	***Digitalis Spp. (all species)***	

No.	Ingredient	Common / Other name
22	***Dioscorea Hispida***	
23	***Dryobalanops lanceolata Burck***	Borneo camphor, Kapur, Malay Camphor, Sumatra camphor
24	***Dryopteris Spp. (all species)***	Mountain woodfern, Spinulose woodfern, Spreading woodfern, Fancy fern
25	***Euphorbia Spp. (all species)***	Spurge
26	***Fritillaria Spp.***	Fritillary Bulb
27	**Gamma-amino Butyric Acid (GABA)**	
28	***Garcinia Morella Desr.***	Gamboge
29	***Gelsemium semperi virens***	Palaung Thay
30	**Glucosamine**	
31	**Glutathione**	
32	***Gypsum Fibrosum***	
33	**Hyaluronic acid**	
34	***Hyoscyamus Spp. (all species)***	
35	***Hypericum perforatum***	St. John's Wort
36	***Juniperus sabina***	Savin, Savine
37	***Mahonia aquifolium, Mahonia repens, Mahonia nervosa***	Mahonia Aquifolium: Oregon Grape, Mountain Grape, Barberry. Mahonia Repens: Creeping Barberry, Creeping Mahonia, Creeping Oregon-Grape
38	***Melanorrhoea usitata Wall.***	Vanish tree
39	***Monascus purpureus***	Red yeast rice
40	***Mucuna pruriens***	Cowhage, Cowage
41	***Mylabris phalerata, Mylabris cichorii***	Blister beatle, Mylabris
42	**Natto extract**	Fermented soybean extract

No.	Ingredient	Common / Other name
43	***Nerium indicum***	Indian oleander, Exile Tree.
44	***Nerium oleander***	Indian oleander, Exile Tree.
45	**Pearl**	
46	***Phellodendron amurense, Phellodendron chinense***	Amur Cork tree
47	**Placenta**	
48	***Plumbago indica***	Rose-coloured leadwort
49	***Plumbago zeylanica***	White leadwort
50	***Psilocybe cubensis***	Boomers, Gold caps
51	***Rauvolfia Spp. (all species)***	
52	**Resveratrol**	
53	***Sanguinaria canadensis***	Bloodroot, Indian Paint
54	***Scilla sinensis***	
55	***Simmondsia Chinesis***	Jojoba
56	***Sophora tomentosa***	Sea coast Laburnum, Silver Bush
57	***Spigelia marilandica***	Worm grass, Pinkroot
58	***Stichopus Spp.***	Gamat
59	***Strophanthus Spp. (all species)***	Kombe
60	***Strychnos ignatii, Strychnos lucida, Strychnos roberans***	Nux-vomica
61	***Symphytum peregrinum***	Comfrey

Notes:

This list :

- is a compilation by the FDI committee.
- is not meant to be exhaustive and will be reviewed from time to time.
- shall be read in conjunction with the current laws and regulations together with other relevant legislations, where applicable, governing pharmaceutical and natural products for human use in Malaysia.

CLASSIFICATION OF FOOD OR DRUG PRODUCTS

	Regulated by FSQD
	Regulated by NPRA
	Classification of FDI under food or drug

PRODUCT

DRUG

1. **Products as defined in Regulation 2, CDCR 1984.**
2. **Products containing 100% active ingredient(s) with or without excipient.**
3. **Products containing specific active ingredients, which possess high pharmacological or therapeutic potencies.** (e.g. paracetamol, glucosamine, tranexamic acid, aspirin, substances listed in Poisons Act 1952).
4. Products containing specific active ingredients, which possess dose-related therapeutic potencies such as:
   - Plant sterols/ stanols and esters that are consumed ≥ 3.5g/day
   - Psyllium husk that are consumed ≥ 3.5g/day
   - Products containing senna ≥ 0.5g
5. **Products in pharmaceutical dosage form** such as soft gel, capsule or tablet (that is to be directly swallowed), sublingual, buccal, spray into the mouth, etc.

1. Products containing ingredient(s) from Negative List For FDI
2. Products not containing ingredient(s) from Negative List for FDI and with medicinal/ health claim
3. Products intended to be used or capable, or purported or claimed to be capable for a medicinal purpose. (e.g. products used for the health benefit of eyes, body weight control, gastrointestine, brain, etc.)

FOOD

1. **100% food ingredients**
2. **Food products with or without active ingredients as below;**
   i) Instant drink products containing sugar and/or creamer (e.g. premix coffee, tea, chocolate, soy, cereal)
   ii) Meat essence products (liquid) (e.g. chicken essence, ostrich essence, duck essence, fish essence, etc.)
   iii) Ready to drink products (beverages) without dose instruction in cheer pack/ cans /packet drinks
   iv) Cordial products with recommended dilution ratio (e.g. dates cordial, grape cordial)
   v) Vinegar products (powder & liquid) (e.g. apple vinegar, dates vinegar, etc.)
   vi) Honey products (powder & liquid)
3. **Isotonic drink products, sport nutrition products and special purpose food products**
4. **Products in conventional food form e.g. biscuit, cake, confectionery, candy/sweet, gummy, noodle**
5. **Products used for cooking and food preparation (e.g. cooking oil (olive oil, coconut oil, sunflower oil), herbs and spices)**
6. **Herbs and spices in crude form without medicinal/health claim**

Products not containing ingredient(s) from Negative List for FDI and without medicinal/ health claim.

APPENDIX 2

MEDICAL DEVICE - DRUG - COSMETIC INTERPHASE (MDDCI) AND COMBINATION PRODUCTS

IMPORTANT NOTES:

This document shall be read in conjunction with the relevant sections of the main guidance document: **Drug Registration Guidance Document (DRGD),** which is in accordance to the legal requirements of the **Sale of Drugs Act 1952** and the **Control of Drugs and Cosmetics Regulations 1984.**

1. INTRODUCTION

a) Medical Device-Drug-Cosmetic Interphase (MDDCI) products are products not clearly defined as a medical device, drug or cosmetic in accordance with the Medical Device Act 737, Control of Drugs and Cosmetics Regulations 1984 and Sale of Drugs Act 1952. It is important to determine whether the products are regulated as medical device, drug or cosmetic because different regulatory requirements apply.

b) Combination products include:

i. A product comprising of two or more regulated components, i.e., drug/device, biological/device, or drug/device/biological, that are physically, chemically, or otherwise combined or mixed and produced as a single entity; OR

ii. Two or more separate products packaged together (co-packaged) in a single package or as a unit and comprised of drug and device products, device and biological products.

c) Products that are excluded from the term "combination product" and will be regulated separately:

i. A drug, device, or biological product packaged separately that according to its investigational plan or proposed labelling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product labelling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or

ii. Any investigational drug or device packaged separately that according to its proposed labelling is use only with another individually specified investigational drug, device or cosmetic product where both are required to achieve the intended use, indication or effect.

iii. Convenience pack product (e.g., first aid kit consists of medical device and non-scheduled poison product)

iv. Natural products and Health Supplement products

d) MDDCI and Combination Products (Device-Drug or Drug-Device) will be regulated by the relevant agencies according to the classification that has been made.

e) The registration of drug/ medical device and notification of cosmetics that have been classified must follow the requirements that have been set forth as follows:

i. **Drugs and Cosmetics** – The registration / notification regulated by the NPRA is in accordance with the requirements set forth in the Poisons Act 1952 and its Regulations, Sale of Drugs Act 1952 and the Control of Drugs and Cosmetics Regulations 1984;

ii. **Medical Device** – The registration regulated by Medical Device Authority is in accordance with the requirements set forth in the Medical Device Act 2012 (Act 737).

f) Please also refer to:

(i) Guideline for Registration of Drug-Medical Device and Medical Device-Drug Combination Products

(ii) *Bil. (6) dlm.BPFK/PPP/01/03Jld.4*
Pekeliling Keperluan Acknowledgement Receipt/ Endorsement Letter *bagi Pendaftaran Baru/ Pendaftaran Semula Produk Kombinasi Ubat-Peranti Perubatan* (Drug-Medical Device Combination) (11 October 2019)

(iii) *Bil. (3) dlm.BPFK/PPP/01/03Jld.4*
Pekeliling Lanjutan Tarikh Pelaksanaan Pemakaian Guideline for Registration of Drug-Medical Device and Medical Device-Drug Combination Products (22 December 2017)

(iv) *Bil. (9) dlm.BPFK/PPP/07/25 Jld.1*
Direktif Kuatkuasa Pemakaian Guideline for Registration of Drug-Medical Device and Medical Device-Drug Combination Products (10 March 2017)

(v) *Bil. (21) dlm.BPFK/PPP/01/03Jld.3*
Pekeliling Mengenai Pengkelasan Semula Produk-produk Daripada Kategori Ubat (Drug) *Kepada Kategori Peranti Perubatan* (Medical Device) (9 December 2014)

2. CLASSIFICATION CRITERIA

The following criteria may be used to assist in the classification of products:

a) The primary intended purpose of the product;

b) The primary mode of action/ the principal mechanism of action by which the claimed effect or purpose of the product is achieved;
   - Drug is based on pharmacological, immunological or metabolic action in/ on the body; but
   - Medical device does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but may be assisted in its intended function by such means;

c) Active ingredient, indication and pharmaceutical dosage form (these are the main criteria for classification of drugs);

d) Classification of the product in reference countries.

For classification of MDDCI and Combination Products refer to **Table I**.

Applicant may verify the product classification with NPRA to determine if the product shall be registered with the Authority or otherwise.

Table I: MEDICAL DEVICE-DRUG-COSMETIC INTERPHASE (MDDCI) AND COMBINATION PRODUCTS CLASSIFICATION DECISION

NO.	PRODUCT	INTENDED PURPOSE/ INDICATION AND MODE OF ACTION (MOA)	CATEGORY	CUSTODIAN DIVISION
1.	**Aqueous Cream Product**	As an emollient cream with moisturizing properties to promote healing and relief to the symptoms of skin dryness, impaired barrier function, skin problems/ diseases.	**OTC DRUG**	**NPRA**
2.	**Blood Bag Containing Anticoagulant/ Preservation Agent**	To collect and preserve blood and its components (for use with cytapheresis device only) **NOTE :** It is not for direct intravenous infusion.	**MEDICAL DEVICE**	**MDA**
3.	**Catheter Lock/ Flush Solutions** (e.g. heparinised saline, sodium citrate solution)	As an anticoagulant for use as a catheter lock/ flush solution for flushing off catheters and cannulas to maintain catheter/ cannula patency and to prevent coagulation of blood or infection in the catheter. **NOTE :** It is not indicated for therapeutic use. Contraindicated for direct systemic administration.	**MEDICAL DEVICE**	**MDA**

NO.	PRODUCT	INTENDED PURPOSE/ INDICATION AND MODE OF ACTION (MOA)	CATEGORY	CUSTODIAN DIVISION
4.	**Collagen Hemostatic Agents** (fibrillar or soft, pliable pad/ sponge or loose fibres)	A sterile, bioabsorbable device derived from animal collagen (e.g., bovine or porcine collagen) designed to produce a rapid haemostasis through platelet activation/ aggregation (which initiates the haemostatic cascade leading to a fibrin clot) during a surgical procedure. It is applied directly to the wound where it remains to be absorbed by the body; it is not dedicated to a specific anatomy/ application and does not contain an antimicrobial agent.	**MEDICAL DEVICE**	**MDA**
5.	**Dental Products**			
	i. Fluoride Dental Preparations (e.g., toothpaste, tooth powder, mouthwash, dental varnish/ suspension)	a. To maintain oral hygiene.	**COSMETIC (If concentration of fluoride ≤1500ppm)**	**NPRA**
		b. To maintain oral hygiene and prevent oral diseases based on pharmacological, immunological or metabolic action.	**DRUG**	**NPRA**
		c. A liquid substance used for the protection of pulpal tissue and to provide a marginal seal to newly placed amalgam restorations. A thin coating of this solution is applied over the tooth's surfaces before placement of restorations. It is used as a protective agent for the tooth against constituents of restorative materials. After application, this device cannot be reused.	**MEDICAL DEVICE**	**MDA**

NO.	PRODUCT	INTENDED PURPOSE/ INDICATION AND MODE OF ACTION (MOA)	CATEGORY	CUSTODIAN DIVISION
		d. As a desensitizing agent for the treatment of hypersensitive teeth, for sealing the dentinal tubules for cavity preparations or on sensitive root surfaces or to line cavity preparations under amalgam restorations.	**MEDICAL DEVICE**	**MDA**
	ii. <u>Root Canal Filling Incorporating Antibiotic</u>	To seal the canal and disinfect the dentinal walls by diffusing through dentine. The antibiotic provides ancillary actions as bactericidal antibiotic and anti-inflammatory agent to assist in reducing pain and in maintaining a bacteria-free environment within the root canal.	**Device-Drug combination product regulated as MEDICAL DEVICE**	**MDA**
	iii. <u>Oral Wound Dressing, Non – Animal/ Microbial Derived</u> (e.g., gel, paste, fluid, spray solution of water/oil)	A compound intended as a protective cover for the oral mucosa to manage wounds and sores in the mouth. It may also be used to treat mucosal irritations/ inflammation, dryness and gingivitis.	**MEDICAL DEVICE** (If it contains an active substance with pharmacological, immunological or metabolic primary mode of action, it will be classified as **DRUG)**	**MDA**
6.	**<u>Dialysis Products</u>**			
	i. <u>Peritoneal Dialysis Dialysate</u>	It is used for the exchange of solutes across the peritoneum of the patient (in this case, used as a semi-permeable membrane)	**DRUG** For continuous ambulatory peritoneal dialysis (CAPD) products with CAPD system (e.g., dialysate bag, drainage bag, transfer tubing, linking	**NPRA**

NO.	PRODUCT	INTENDED PURPOSE/ INDICATION AND MODE OF ACTION (MOA)	CATEGORY	CUSTODIAN DIVISION
			connector, disc, injection port, overpouch etc.), it will be classified as **Drug-device combination product and shall be regulated as DRUG (refer to No.9. Drug - Delivery Products Regulated as Drug Products)**	
	ii. Haemofiltration Solution	It is used for the exchange of solutes with blood through a system of extracorporeal filters.	**DRUG**	**NPRA**
	iii. Haemodialysis Dialysate	It is used for the exchange of solutes with blood through a semi-permeable membrane in the dialyser of a haemodialysis system.	**MEDICAL DEVICE**	**MDA**
	iv. Haemodiafiltration Solution	It is used as a replacement solution in haemodiafiltration. **NOTE :** Haemodiafiltration is the combination of haemodialysis and haemofiltration performed either simultaneously or sequentially.	**DRUG**	**NPRA**

NO.	PRODUCT	INTENDED PURPOSE/ INDICATION AND MODE OF ACTION (MOA)	CATEGORY	CUSTODIAN DIVISION
7.	**Drug-Eluting Beads** (Produced from biocompatible polyvinyl alcohol hydrogel modified with sulphonate groups in phosphate buffered saline)	It is an embolic agent which is intended to be loaded with a chemotherapy agent, e.g., doxorubicin for the purpose of treatment of malignant hypervascularised tumour(s) by embolisation of vessels and occlusion of blood flow supplying malignant hypervascularised tumour(s) and as a secondary action, delivers/elutes a local, controlled, sustained dose of the chemotherapy agent directly to the tumour(s).	If the beads are sold separately from the drug, it will be classified as **MEDICAL DEVICE** If the beads and drug are packaged and sold together, it will be classified as **Drug-device combination product and shall be regulated as DRUG**	**MDA/NPRA**
8.	**Drug-Eluting Stents (DES)**	For use in angioplasty or coronary stenting procedures.	**Device-Drug combination product regulated as MEDICAL DEVICE**	**MDA**
9.	**Drug - Delivery Products Regulated as Drug Products** (e.g., insulin prefilled pen/ syringes, asthma inhalers, intrauterine with hormone action, CAPD products with CAPD system (e.g., dialysate bag, drainage bag, transfer tubing, linking connector, disc, injection port, overpouch etc.)	To administer pharmacologically active substance	**Drug-device combination product regulated as DRUG**	**NPRA**

NO.	PRODUCT	INTENDED PURPOSE/ INDICATION AND MODE OF ACTION (MOA)	CATEGORY	CUSTODIAN DIVISION
10.	**Enteral Feeding Kit** (containing Iodine Pack drug)	A collection of sterile devices that includes tubing and other materials intended to administer nutrient liquids directly into the stomach, duodenum, or jejunum of a patient by means of gravity or an enteral pump.	**Device-Drug combination product regulated as MEDICAL DEVICE**	**MDA**
11.	**Eye Products**			
	i. Eye/Ocular Lubricants, Including Artificial Tears	A sterile substance used to provide supplemental lubrication/ hydration/ moisturization to the eyes to treat/ alleviate symptoms of soreness, burning, irritation and discomfort caused by dry, tired, and/ or strained eyes resulting from dry eye syndrome, ageing/ hormone changes (menopause), or environmental factors (e.g., pollution, dust, heat, smoke and air conditioning).	**MEDICAL DEVICE** (If it contains an active substance with pharmacological, immunological or metabolic primary mode of action, it will be classified as **DRUG)**	**MDA**
	ii. Aqueous/Vitreous Humour Replacement Medium	It is used to assist in performing ophthalmic surgery, e.g., to maintain the shape of the eyeball during the intervention, preserve tissue integrity, protect from surgical trauma, or to function as a tamponade during retinal reattachment.	**MEDICAL DEVICE**	**MDA**

NO.	PRODUCT	INTENDED PURPOSE/ INDICATION AND MODE OF ACTION (MOA)	CATEGORY	CUSTODIAN DIVISION
	iii. **Cold Sensation Eye Pillow**	To reduce fatigue from work stress or lack of sleep.	**MEDICAL DEVICE**	**MDA**
12.	**General Purpose Surgical or Barrier Drapes** (A sterile protective covering made of natural or synthetic materials, or both)	To isolate a site of surgical incision or a surgical field from contamination (e.g., microbial, substance) in various clinical settings (e.g., in an operating room or catheterization laboratory). The device may also be used to protect a patient from heat/flame during a surgical procedure. This is a reusable or single use device.	**MEDICAL DEVICE** (If it incorporates an ancillary pharmacologically active substance, it will be classified **as Device-Drug combination and shall be regulated as MEDICAL DEVICE)**	**MDA**
13.	**General-Body Orifice Lubricant**	Lubricant intended to facilitate entry of a diagnostic or therapeutic device into a body orifice by reducing friction between the device and the body; Lubricant during catherisation, probing, endoscopy, changing fistula catheters, intubation, and prevention of iatrogenic injuries to the rectum and colon. E.g., ancillary local anaesthetic: lidocaine	**MEDICAL DEVICE** (If it incorporates an ancillary pharmacologically active substance, it will be classified **as a Device-Drug combination product and shall be regulated as MEDICAL DEVICE**	**MDA**
14.	**Head Lice Products**	a. Acts solely by coating and/ or suffocating the lice and/ or its eggs	**MEDICAL DEVICE**	**MDA**

NO.	PRODUCT	INTENDED PURPOSE/ INDICATION AND MODE OF ACTION (MOA)	CATEGORY	CUSTODIAN DIVISION
		b. Disrupting the water balance mechanism of the lice by dissolving and emulsifying off their protective cuticular lipid layer, alters physical characteristics of the egg so that the nymph develops to maturity but cannot hatch.	**MEDICAL DEVICE**	**MDA**
		c. To coat the hair in a film that deters lice from transferring from an infected head to the one treated	**MEDICAL DEVICE**	**MDA**
15.	**<u>Heat Pad/ Cooling Pad</u>**	To relief aches and pains.	**MEDICAL DEVICE**	**MDA**
16.	**<u>In Vivo Diagnostic Agents</u>**	a. Topical/intraocular/intravitreal ophthalmic staining agents/ dyes for diagnostic purpose, enhance visualization during ophthalmic procedures and/or contact lens fitting; e.g., fluorescein ophthalmic strips, trypan blue, brilliant blue, methylene blue.	**MEDICAL DEVICE**	**MDA**
		b. For diagnostic purposes other than No.16a, such as: - Intravenous Fluorescein dye for ophthalmic angiography, e.g., Fluorescein injection - X-ray/ MRI contrast media - NMR enhancing agents - Carrier solutions to stabilize microbubbles for ultrasound imaging	**DRUG**	**NPRA**

NO.	PRODUCT	INTENDED PURPOSE/ INDICATION AND MODE OF ACTION (MOA)	CATEGORY	CUSTODIAN DIVISION
		- Radiopharmaceuticals for diagnostic use (e.g., 14C- Urea Capsule for H pylori test) - Hapten preparation for the diagnosis of contact allergy		
		c. As Diagnostic Test Kit consist of drug and analyser	**DRUG-DEVICE combination product regulated as DRUG** **NOTE:** The device component will be regulated on a case to case basis.	**NPRA**
		d. As diagnostic analyser only (without drug)	**MEDICAL DEVICE**	**MDA**
17.	**<u>Irrigation Solutions</u>**	For mechanical cleansing and rinsing including those used in the eye such as for cleansing of the eye, body tissues, body cavities, wounds or irrigation of a special tube called a catheter which is used to drain the bladder.	**MEDICAL DEVICE** (If it contains a pharmacologically active substance, it will be classified as **DRUG)**	**MDA**
18.	**<u>Local Refrigeration Anaesthesia</u>**	Used as local anaesthetic due to intense cold produced by instant evaporation e.g., in minor operative procedures or to alleviate pain associated muscle injuries etc; of which results in insensitivity of peripheral nerve endings and a local anaesthesia. Its principal mode of action is not pharmacological, immunological or metabolic.	**MEDICAL DEVICE** (If it contains a pharmacologically active substance, it will be classified as **DRUG)**	**MDA**

NO.	PRODUCT	INTENDED PURPOSE/ INDICATION AND MODE OF ACTION (MOA)	CATEGORY	CUSTODIAN DIVISION
19.	**<u>Medicinal Gases</u>**	a. Gases or gas mixtures which mode of action is achieved primarily based on pharmacological, immunological or metabolic action in/on the body, such as gases for hypoxia (oxygen gas) and anaesthetic (nitrous oxide gas)	**DRUG**	**NPRA**
		b. Gases or gas mixtures which mode of action is achieved primarily by physical in nature and not achieved primarily based on pharmacological, immunological or metabolic action in/on the body, such as gases for insufflation of the abdominal cavity for laparoscopy and gases for removal of warts (e.g., liquid nitrogen).	**MEDICAL DEVICE**	**MDA**
20.	**<u>Medicinal Patch</u>**	To relieve fatigue, body aches, joint pains. To regulate hormone imbalance	**DRUG**	**NPRA**
21.	**<u>Nail Anti-Fungal Products</u>** (e.g., pen applicator containing acetic acid/ lactic acid)	Treatment of onychomycosis (fungal nail infection) by lowering the pH of the nail bed, thus creating a micro-environment that is hostile to fungal growth.	**MEDICAL DEVICE**	**MDA**
22.	**<u>Nasal Inhaler</u>**	To act as a barrier against external influences by formation of a moisturizing film on the nasal mucosa.	**MEDICAL DEVICE** (If it contains a pharmacologically active substance, it will be classified **as DRUG)**	**MDA**

NO.	PRODUCT	INTENDED PURPOSE/ INDICATION AND MODE OF ACTION (MOA)	CATEGORY	CUSTODIAN DIVISION
23.	**Oral Care Products**			
	Artificial Saliva/ Saliva Substitute/ Replacement	Solutions used to mimic and replace/ substitute normal saliva in the symptomatic treatment of dry mouth (xerostomia). Generally, contain viscosity-increasing agents, such as mucins or cellulose derivatives, carmellose as well as electrolytes, including fluoride. They seldom relieve symptoms for more than 1 or 2 hours and does not stimulate saliva production.	**MEDICAL DEVICE**	**MDA**
24.	**Other Topical Antiseptics/ Disinfectants**			
	i. Swabs/ Wipes Containing Antiseptics/ Disinfectants/ Antimicrobial Substances (e.g., chlorhexidine, iodine, cetrimide)	For use on human skin and intended to be used for a medical purpose, e.g., pre/ post injection, wound cleaning etc.	**DRUG**	**NPRA**
	ii. Preparations (Including Swabs/ Wipes) Containing Antiseptics/ Disinfectants/ Antimicrobial Substances (e.g., alcohol, chlorhexidine, iodine, cetrimide)	Intended for the disinfection of medical devices.	**MEDICAL DEVICE**	**MDA**
	iii. Alcohol Only Wipes/ Swabs	To be used for a medical purpose to wipe intact skin for needles access	**MEDICAL DEVICE**	**MDA**

NO.	PRODUCT	INTENDED PURPOSE/ INDICATION AND MODE OF ACTION (MOA)	CATEGORY	CUSTODIAN DIVISION
25.	**<u>Peeling/ Exfoliator Products</u>** (e.g., Products containing glycolic acid and salicylic acid)	To improve skin texture due to unaesthetic skin appearance caused by pigmentation, post acne scars, photo damage, etc. **NOTE:** The ingredient and intended use should comply with the Guidelines for Control of Cosmetic Products in Malaysia.	**COSMETIC**	**NPRA**
26.	**<u>Personal Care Products</u>**			
	i. <u>Personal Intimate Hygiene</u>	a. For female/ male intimate hygiene **NOTE:** The product should be rinsed off.	**COSMETIC**	**NPRA**
		b. For symptomatic relief of vaginal irritation/ infections by changing the vaginal pH.	**MEDICAL DEVICE** (If it contains a pharmacologically active substance, it may be classified as **DRUG)**	**MDA**
	ii. <u>Vaginal Douche</u>	Vaginal douching is the process of intravaginal cleansing with a liquid solution for: - personal hygiene or aesthetic reasons - preventing or treating/ managing vaginal infections	**MEDICAL DEVICE** (If it contains a pharmacologically active substance, it may be classified as **DRUG)**	**MDA**

NO.	PRODUCT	INTENDED PURPOSE/ INDICATION AND MODE OF ACTION (MOA)	CATEGORY	CUSTODIAN DIVISION
		- symptomatic relief of minor vaginal soreness, irritation, itching - cleansing and deodorizing after menstruation - washing out vaginal medication, if so instructed by the physician - deodorizing and washing out the accumulations of normal secretions - removing contraceptive creams and jellies - cleansing the vaginal vault after sexual relations **NOTE:** - Douching is not recommended during pregnancy - A douche is to be used as a cleanser and it should not be used as a contraceptive		
	iii. <u>Hand Sanitizer</u> (e.g., gel, foam, liquid)	For general hand hygiene without therapeutic claims.	**COSMETIC**	**NPRA**
	iv. <u>Personal Intimate Lubricant</u>	To use as a vaginal lubricant during the climaterium (pre-menopause, menopause, post-menopause) and to treat irritations in vaginal epithelium in cases of physiological decrease of lubrication and consequent increase in vaginal dryness.	**MEDICAL DEVICE** (If it contains a pharmacologically active substance, it may be classified as **DRUG)**	**MDA**

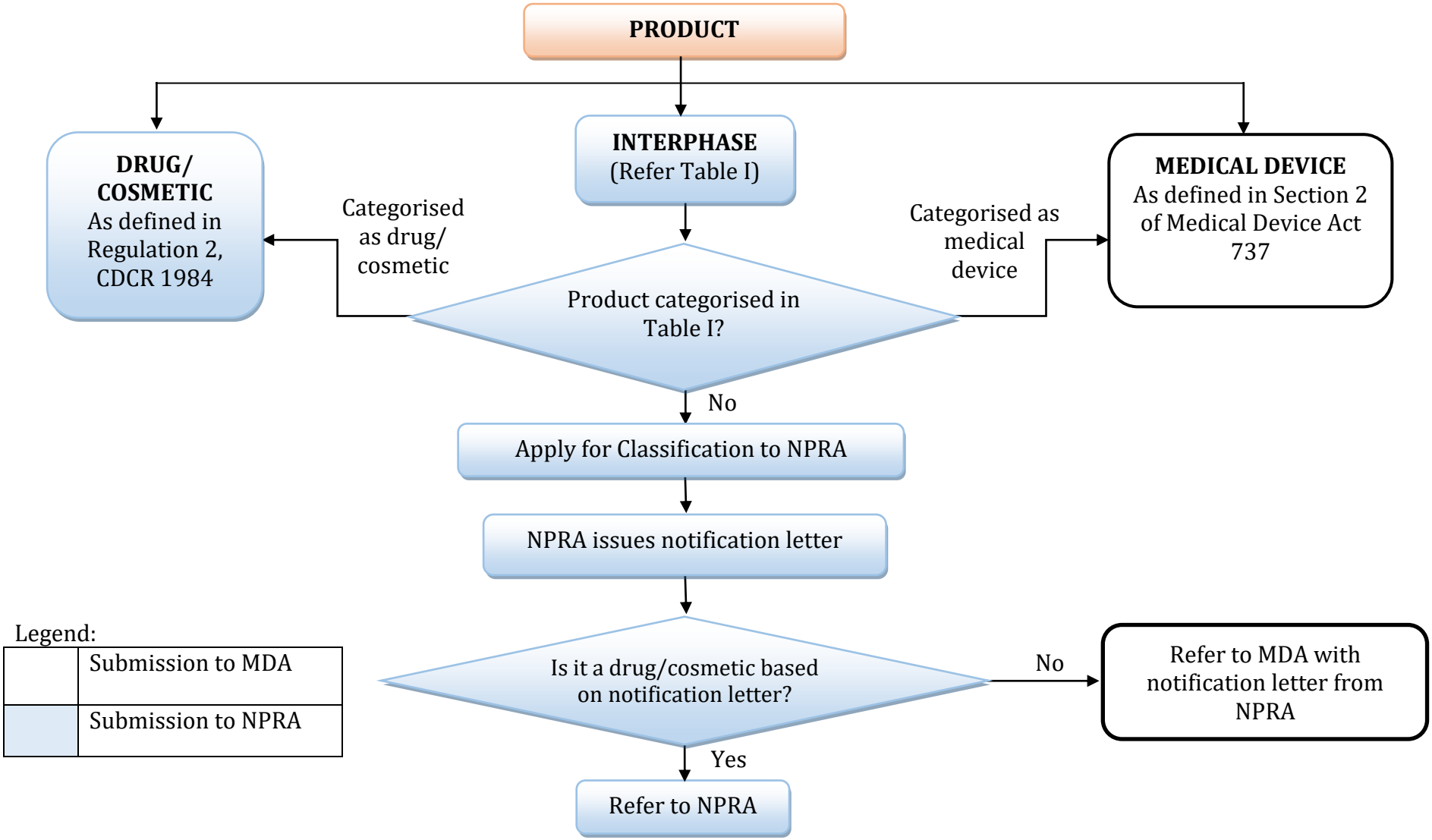
NO.	PRODUCT	INTENDED PURPOSE/ INDICATION AND MODE OF ACTION (MOA)	CATEGORY	CUSTODIAN DIVISION
27.	**<u>Skin Barrier Product</u>** (e.g., lotion, emulsion, ointment, cream)	a. To form a physical barrier between the skin and the environment to seal out moisture in order to promote healing and relief to the symptoms of skin dryness, impaired barrier function, skin problems/ diseases.	**MEDICAL DEVICE** (If it contains a pharmacologically active substance, it may be classified as **DRUG)**	**MDA**
		b. Soothe and prevent diaper rash discomfort.	**DRUG**	**NPRA**
		c. To maintain/ improve normal skin condition without any therapeutic claims.	**COSMETIC**	**NPRA**
28.	**<u>Soft Tissue Filler/ Dermal Filler</u>**	To correct cutaneous contour deformities of the skin (e.g., moderate to severe facial wrinkles and folds such as nasolabial folds, scars), particularly in cases of aging or degenerative lesions.	**MEDICAL DEVICE** (If it incorporates an ancillary pharmacologically active substance, such as local anaesthetic, e.g., lidocaine, it will be classified **as a Device-Drug combination product and shall be regulated as MEDICAL DEVICE)**	**MDA**
29.	**<u>Synthetic Fluid Tissue Reconstructive Material</u>**	As a submucosal implant in the urinary tract for urinary incontinence or vesicoureteral reflux. It may also be injected into the vocal cords to treat the effects of paralysis, atrophy, or scarring. After application, this device cannot be reused.	**MEDICAL DEVICE** (If it incorporates an ancillary pharmacologically active substance, such as local anaesthetic e.g, lidocaine, it will be classified as a **Device-Drug combination product and shall be regulated as MEDICAL DEVICE)**	**MDA**

NO.	PRODUCT	INTENDED PURPOSE/ INDICATION AND MODE OF ACTION (MOA)	CATEGORY	CUSTODIAN DIVISION
30.	**<u>Product For Synovial Joint</u>**	a. Used as synovial fluid replacements where viscosupplementation provides support and lubrication to help cushion the joint, especially in cases of reduced endogenous synovial fluid viscosity from degenerative disease.	**MEDICAL DEVICE**	**MDA**
		b. Elicits pain relief and improvement in osteoarthritis via several complex biochemical actions resulting modulation of cell activity.	**DRUG**	**NPRA**
31.	**<u>Wart Products</u>** (e.g., pen applicator containing a caustic agent, cyryogenic kit with refrigerant)	a. Containing a caustic agent e.g., trichloroacetic acid (TCA) that destroys warts by chemical coagulation of proteins.	**DRUG** **NOTE:** If a device component is present, it will be regulated on a case to case basis	**NPRA**
		b. Cryotherapy that destroys warts by freezing them using a very cold substance e.g., liquid nitrogen or refrigerant made from dimethyl ether and propane.	**MEDICAL DEVICE**	**MDA**
32.	**<u>Wound Care/ Treatment Products</u>**			
	i. <u>Comprising A Matrix</u> (e.g., dressing, gauze, swabstick, plaster, sponge)	a. To administer a medicinal substance to the wound, e.g. antimicrobial/ antiseptic agent for the purpose of controlling infection.	**DRUG**	**NPRA**

NO.	PRODUCT	INTENDED PURPOSE/ INDICATION AND MODE OF ACTION (MOA)	CATEGORY	CUSTODIAN DIVISION
		b. To provide a protective layer/barrier to the wound and prevent microbial penetration and create healing environment. It may incorporate an ancillary medicinal substance e.g., antimicrobial/ antiseptic agent.	**MEDICAL DEVICE**	**MDA**
	ii. <u>Comprising A Matrix, Typically Of Living Cells (Fibroblasts) And/ Or Structural Proteins</u>	To facilitate the infiltration of native skin elements (e.g., fibroblasts, leukocytes, blood vessels) for skin regeneration.	**MEDICAL DEVICE**	**MDA**
	iii. <u>Topical Preparation For Application To A Skin Wound</u> (e.g., abrasion, laceration, cut, ulcer)	To facilitate local haemostasis. It is available in various forms (e.g., gel, spray, powder, ointment, plaster/gauze pad) that can be applied directly to the wound where it forms a seal of transparent layer.	**MEDICAL DEVICE**	**MDA**
	iv. <u>Deep Cavity Wounds Dressing For Application To A Surgical Wound</u>	To use as the wound covering material for deep body cavity to reduce the adhesion of surrounding tissues by applying to the surgical area.	**MEDICAL DEVICE**	**MDA**
	v. <u>Silver-Containing Topical Preparations For Application To A Skin Wound</u> (e.g., silver nitrate/ silver sulfadiazine/ colloidal silver gel, cream)	a. To administer/ apply an antiseptic/ antimicrobial to wounds for the purpose of treating infection	**DRUG**	**NPRA**

NO.	PRODUCT	INTENDED PURPOSE/ INDICATION AND MODE OF ACTION (MOA)	CATEGORY	CUSTODIAN DIVISION
		b. Treatment of wounds by creating a viscoelastic and lubricated environment and providing a protective barrier at the level of the lesion, for natural wound healing, of which the silver acts as ancillary medicinal substance	**MEDICAL DEVICE**	**MDA**
	vi. <u>Intravascular Catheter Securement Device Containing Antimicrobial/ Antiseptic Agent</u> (e.g., chlorohexidine gluconate, CHG)	An intravascular catheter securement device is a device with an adhesive backing that is placed over a needle or catheter and is used to keep the hub of the needle or the catheter flat and securely anchored to the skin. The antimicrobial agent provides ancillary antimicrobial activity to reduce skin colonization and catheter colonization, suppress regrowth of microorganism's, and reduce catheter-related bloodstream infections (CRBSI) in patients with central venous or arterial catheters.	**DEVICE-DRUG combination product regulated as MEDICAL DEVICE**	**MDA**

GUIDANCE FOR THE CLASSIFICATION OF MEDICAL DEVICE-DRUG-COSMETIC INTERPHASE (MDDCI) PRODUCTS



APPENDIX 3

GUIDELINE ON REGISTRATION OF NEW DRUG PRODUCTS

IMPORTANT NOTES:
This document shall be read in conjunction with the relevant sections of the main guidance document: **Drug Registration Guidance Document (DRGD)**, which is in accordance to the legal requirements of the **Sale of Drugs Act 1952** and the **Control of Drugs and Cosmetics Regulations 1984**.

1. DEFINITION

New Drug Products (NDP) is defined as any pharmaceutical products that have not been previously registered in accordance with the provisions of the CDCR 1984.

An NDP may be classified according to the following categories:

1.1 New Chemical Entity (NCE) (single/ combination products with an active substance never registered by DCA)

Defined as an **active moiety**/ radiopharmaceutical substance that has not been registered in any pharmaceutical product.

An **active moiety** is defined as the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds) or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

A radiopharmaceutical substance is defined as a radionucleotide, ligand or the coupling mechanism to link the molecule and the radionucleotide that has not been registered in any pharmaceutical product.

1.2 Hybrid (single/ combination products with registered active moieties)

All other products registrable at New Drug Section which do not fall under **(1.1)**.

Examples of Hybrid (single/ combination) products:

i. Registered chemical entity(s) in a new chemical form(s)
ii. Registered chemical entity(s) in a new dosage form(s)
iii. Registered chemical entity(s) in a new dosage strength(s) with a change in dosing/ posology
iv. Registered chemical entity(s) for use by a new route of administration
v. Registered chemical entity(s) for new indication(s), dosage recommendation(s) and/ or patient population(s)
vi. Combination of registered chemical entity(s) in new chemical form(s) and registered chemical entity(s)
vii. A product for which its innovator has never been registered by DCA
viii. Second source product
ix. Replacement product

For medicinal gases classified as new drug products, please refer to Directive No. 8, 2021 and Guideline on Registration of Medicinal Gases.

Reference:

- Directive No. 8, 2021, NPRA.600-1/9/13 (18): *Direktif Berkenaan Pengukuhan Pelaksanaan Kawalan Regulatori Ke Atas Produk-Produk Gas Perubatan dan Penggunaan Guideline on Registration of Medicinal Gases* (11 February 2021)

2. REGISTRATION REQUIREMENT AND EVALUATION TIMELINE

Table 1: Registration Requirement and Evaluation Timeline for NDP

ITEMS	REGISTRATION REQUIREMENTS	
	HYBRID	NCE
ACTD Module:		
1) Part I	Yes	Yes
2) Part II (S)[1]	Yes	Yes
3) Part II (P)	Yes	Yes
4) Part III	No[2]	Yes[3]
5) Part IV	BA/BE/pivotal study report(s), clinical overview and RMP	Full, including RMP
	HYBRID	**NCE**
Consultation with local clinical specialists[4]	No[5]	Yes
Evaluation timeline	210 working days	245 working days

[1] Please refer to "GUIDANCE NOTES: ACTIVE PHARMACEUTICAL INGREDIENT (API) INFORMATION (PART II S) FOR QUEST3+ PRODUCT REGISTRATION APPLICATION",

which outlines the requirements when preparing submission of a new product application using the same source of an approved API of a registered product; API evaluation is manufacturer and PRH specific.

[2] Non-clinical overview only, if applicable.

[3] Good Laboratory Practice (GLP) Compliance Form is to be submitted at E14 during initial evaluation (screening process).

[4] Selected clinical publications/ study synopsis are sent to local clinical specialists to gather comments on product efficacy and safety.

[5] Consultation with local clinical specialists is required for a product for which its innovator has never been registered by DCA and other hybrid application, when deemed necessary.

NOTE:

For a product in which the reference innovator product has never been registered in Malaysia, **specific requirements for Parts III and IV**:

i. Nonclinical Overview, Nonclinical Summary & List of Key Literature References, by referring to studies by the innovator product
ii. Clinical Overview, Clinical Summary & List of Key Literature References, by referring to studies by the innovator product
iii. Bioequivalence study report(s)
iv. Other pivotal study reports, if applicable
v. Risk Management Plan (RMP)
vi. Consultation with local clinical specialists

APPENDIX 4

GUIDELINE ON REGISTRATION OF BIOLOGICS

IMPORTANT NOTES:

This document shall be read in conjunction with the relevant sections of the main guidance document: **Drug Registration Guidance Document (DRGD)**, which is in accordance to the legal requirements of the **Sale of Drugs Act 1952** and the **Control of Drugs and Cosmetics Regulations 1984**.

The National Pharmaceutical Regulatory Agency (NPRA) requirements for registration of biologics/ biopharmaceuticals products are aligned with the scientific guidelines and recommendations for quality, clinical efficacy and safety and non-clinical of the **World Health Organization (WHO), European Medicines Agency (EMA) and International Conference of Harmonization (ICH).**

Where appropriate, the relevant WHO, EMA and ICH guidelines on biologics/ biopharmaceuticals shall be consulted.

- WHO (*https://www.who.int /*)
- EMA (*http://www.ema.europa.eu*)
- ICH (*http://www.ich.org*)

Every biologic is regulated as a new product and also considered 'high risk'. Both drug substance and drug product production must comply to Good Manufacturing Practice strictly. Adoption of GMP as an essential tool of Quality Assurance System.

The requirements for registration of biologics/ biopharmaceuticals shall be in accordance to the **ASEAN Common Technical Dossier (ACTD)** format and in adherence to the general regulatory requirement as described in sections of the main DRGD. It covers:

- Administrative information
- Product quality data
- Product safety data
- Clinical data, demonstrating clinical efficacy and capacity to meet therapeutic claims, through clinical studies

Animal derived materials/ products are commonly used in the manufacture of biologics/ biopharmaceuticals. A detailed information regarding the rationale for use of such material e.g. the source, etc. shall be provided, as per **Checklist A** and **Checklist B**; and also provide a confirmation on the presence/ absence of the animal materials in the final product.

This document is intended to provide guidance for the registration of biologics. However, this document will serve as a living document that will be updated/ revised further in line with the progress in scientific knowledge and experience.

Note: This document is not intended to apply to the control of genetically-modified live organisms designed to be used directly in humans, e.g. live vaccines.

Outline:

1. GENERAL INFORMATION

1.1 Definitions

1.2 Introduction

2. SPECIFIC REQUIREMENTS FOR REGISTRATION OF BIOLOGICS

2.1 Requirements for Registration of Vaccines and Biotechnology Products

2.1.1 Vaccines

(i) Definition of Vaccine

(ii) Requirements for Registration of Vaccines (Chemistry, Manufacturing and Control [CMC])

2.1.2 Biotechnology Products

(i) Definition of Biotechnology Product

(ii) Additional Requirements for Registration of Biotechnology Products

2.1.3 References

2.2 Requirements for Registration of Blood Products

2.2.1 Definition of Blood Product

2.2.2 Requirements for Registration of Blood Products

2.2.3 Checklist of Plasma Master File for Blood Products

2.2.4 References

3. CHECKLISTS OF REGISTRATION FOR PRODUCTS CONTAINING MATERIALS OF ANIMAL ORIGIN

3.1 Checklist A: Products Containing Animal-Derived Materials **with** a valid TSE risk evaluation Certificate of Suitability (CEP)

3.2 Checklist B: Products Containing Animal-Derived Materials **without** a valid TSE risk evaluation Certificate of Suitability (CEP)

1. GENERAL INFORMATION

1.1 DEFINITIONS

i) Biopharmaceutical/ Biotechnology Product
ii) Biologic/ Biological Product

The term 'biopharmaceutical' was coined in the 80's to define proteins that were made by recombinant DNA technology [which includes hybridoma technology for monoclonal antibody (mAb) production].

Biologic/ Biological product refers to a product whose active substance is made by or derived from a living organism (plant, human, animal or microorganism) and may be produced by biotechnology methods and other cutting-edge technologies. This product imitates natural biological substances in our bodies such as hormones, enzymes or antibodies.

Biological substance is defined as a substance that is produced by or extracted from a biological source and that needs, for its characterization and the determination of its quality, a combination of physicochemical-biological testing together with the production process and its controls.

Biopharmaceuticals/ Biologics/ Biological products can also be defined as:
"A protein (including antibodies) or nucleic acid-based pharmaceuticals used for therapeutic, which is produced by means other than direct extraction from a native (non-engineered) biological source". This corresponds to the new biotechnology view (that is, by elimination, it is largely restricted to recombinant/ genetically engineered and mAb-based products).

The term 'Biotechnology product' and 'Biological product' are used to broadly refer to all biopharmaceuticals (by the broad biotechnology view).

Note:
Today, biologics have become inextricably intertwined with biopharmaceuticals, to the point where they are synonymous. The general consensus is that a 'Biologic' and 'Biopharmaceutical' are interchangeable terminology, but a biologic might incorporate some other products (e.g. allergenics, somatic cells etc.).

Biologics <u>include</u> a wide range of products such as:

1. Vaccines;
2. Blood products;
3. Monoclonal antibodies (therapeutics);
4. Recombinant proteins:
   - Insulins
   - Hormones
   - Erythropoetins and other hematopoietic factors
   - Cytokines: interferons, interleukins, colony-stimulating factors, tumour necrosis factors

5. Cell and Gene Therapy Products (CGTPs)

But do <u>not include</u>:

1. Metabolites from microorganisms; e.g. antibiotics and some hormones.
2. Macromolecules produced by chemical synthesis; e.g. peptides/ oligonucleotides produced by chemical synthesis.
3. Whole blood or cellular blood components.

Unlike small-molecule generic drugs, exact copies of biologics are impossible to produce because these are large and highly complex molecules produced in living cells. A 'biosimilar' medicinal product (a short designation for 'similar biological medicinal product') is considered as a new biological medicinal product developed to be similar in terms of quality, safety and efficacy to an already registered, well established, medicinal product. For details, please refer to Guidance Document and Guidelines for Registration of Biosimilars in Malaysia.

Cell and Gene Therapy Products (CGTPs) are regulated as Biologic products. Unlike biotechnology products which are mostly purified proteins of cells, CGTPs contain living and functional cells. Therefore, CGTP is regulated under a separate framework.

For details, please refer to Guidance Document and Guidelines for Registration of Cell and Gene Therapy (CGTPs) in Malaysia. This document provides information for manufacturers, applicants, healthcare professionals and the public on legal arrangements in Malaysia for the registration of CGTPs. The implementation of the guideline will be compulsory on 1 January 2021 as stated in Directive No. 6, 2017. Please also refer to Directive No. 19, 2020 regarding the details of mechanism for registration and enforcement of CGTPs in stages.

References:

i) Directive No. 19, 2020. *NPRA.600-1/9/13(10) Direktif Berkenaan Pelaksanaan Pendaftaran Produk dan Penguatkuasaan Secara Berperingkat Bagi Produk Terapi Sel dan Gen (CGTPs) Serta Tambahan Senarai Produk Di Luar Skop Kawalan CGTPs Oleh PBKD* (14 December 2020)

ii) Directive No. 6, 2017. *BPFK/PPP/07/25(11) Jld.1* *Direktif Untuk Menguatkuasakan Penggunaan* Guidance Document and Guidelines for Registration of Cell and Gene Therapy Products (CGTPs), December 2015 dan Good Tissue Practice Guideline, 2nd Edition, December 2015 (29 May 2017)

iii) Good Tissue Practice Guideline, 2nd Edition, December 2015

1.2 INTRODUCTION

It is acknowledged that biological substances used in the practice of medicines make a vital contribution to health care. Nevertheless, because of their nature, biologicals demand special attention with regard to their regulations to assure quality, efficacy and safety.

Biologicals are inherently variable due to their biological nature, produced from biological materials, and often tested in biological test systems, themselves variable, a feature that has important consequences for the safety and efficacy of the resulting product. Each product must be evaluated on its own merits. A prerequisite for the use of biological is therefore to assure the consistency of quality and safety from lot-to-lot.

Today, the biological field is one of enormous expansion and increasing diversity, most especially in the area of new biotechnologies. The revolution of DNA-based and other cell technologies has opened up a new and exciting vista, and in many instances, traditional products are being replaced by equivalents derived by recombinant DNA technologies or other cutting-edge technologies.

It is important to note that the demonstration that a product consistently possesses a desired characteristics of safety and efficacy will depend on a multifaceted approach on the part of manufacturer and the regulatory authority - drawing on thorough characterization of starting materials, demonstration of consistency of production, and appropriate selection of lot release tests - all under the stringent and documented controls imposed by good manufacturing practices - as well as rigorous post marketing surveillance activities.

2. SPECIFIC REQUIREMENTS FOR REGISTRATION OF BIOLOGICS

2.1 REQUIREMENTS FOR REGISTRATION OF VACCINES AND BIOTECHNOLOGY PRODUCTS

2.1.1 Vaccines:

(i) Definition of Vaccine

A vaccine contains an active component (the antigen). A vaccine is an immunogen, the administration of which is intended to stimulate the immune system to result in the prevention, amelioration or therapy of any disease or infection.

Vaccines for human use include one or more of the following:

a) microorganisms inactivated by chemical/ physical means that retain appropriate immunogenic properties;
b) living microrganisms that have been selected for their attenuation whilst retaining immunogenic properties;
c) antigen extracted from microorganisms, secreted by them or produced by recombinant DNA technology; or
d) antigen produced by chemical synthesis *in vitro*.

The antigens may be in their native state, truncated or modified following introduction of mutations, detoxified by chemical or physical means and/or aggregated, polymerized or conjugated to a carrier to increase immunogenicity. Antigens may be presented plain or in conjunction with an adjuvant, or in combination with other antigens, additives and other excipients.

(ii) Requirements for Registration of Vaccines (Chemistry, Manufacturing and Controls [CMC])

A.	DESCRIPTION
	▪ Description - Information on the source materials: source materials include any component/ unformulated active substance used in the manufacture of the product (e.g microorganisms, cells/ cell subtrate, immunogen) including their specifications and the tests used to demonstrate compliance with the specifications. For combination vaccines, each active substance, which will be pooled, combined with other antigens and formulated, shall be described. ▪ Any chemical modification or conjugation of the drug substance shall be described in detail. ▪ List of inactive substances, which may be present in the drug substance.
B.	**METHOD OF MANUFACTURE/ PRODUCTION**
1.	**Manufacturing Formula:** ▪ List of all materials (culture media, buffers, resins for peptide synthesis, chemicals, columns etc.) and their tests and specifications, or reference to pharmacopoeia. ▪ Complete formula inclusive of any adjuvants, diluents, preservatives, additives, stabilisers etc. ▪ Production of each antigen in the vaccine (i.e. fermenter or culture volumes for each bulk batch size as applicable and typical bulk volumes per production run). ▪ Batch formula for each batch size and final formulated bulk product. ▪ Lot numbering system for intermediates and final product.
2.	**Manufacturing Process:** **Flow Charts/ Diagrams be Accompanied by a Descriptive Narrative:** ▪ Detailed description of manufacturing process and characterization of the product. Include complete history and characterization/ characteristics of each species, strain, cell banking systems - Master Cell bank (MCB) and Working Cell Bank (WCB), cell/ seed lot system, cell substrate system, animal sources (including fertilized avian eggs), virus source or cellular sources. **Reference:** WHO TRS 878 (1998) *Annex 1: Requirements for the use of animal cells as in vitro substrates for the production of biologicals.* ▪ The flow chart should show the steps in production and a complete list of the in-process controls and tests performed on the product at each step. ▪ In-process holding steps, with time and temperature limits indicated. ▪ Description of the manufacturing processes (flow diagram) in detail to support the consistency of manufacture of drug substance - cell growth and harvesting. ▪ Identification of any processes or tests performed by contract manufacturers or testers.

	▪ Animal cells: Cells of animal origin may harbour adventitious agents and consequently pose a potentially greater risk to humans. Description of measures taken to remove, inactivate, or prevent contamination of the product from any adventitous agent present. ▪ Information on measures to prevent any catastrophic events that could render the cell banks unusable and to ensure continuous production of vaccines is crucial. For recombinant vaccines: description of the construction and characterization of the recombinant vector as well as source of master cell bank/ constructs.
3.	**Process Validation Program:** ▪ Describe general policy for process validation and provide process validation activities performed.
4.	**Handling, Storage and Packaging:** ▪ All arrangements for the handling of starting materials, packaging materials, bulk and finished products, including sampling, quarantine, release and storage.
C.	**QUALITY CONTROL**
1.	**Starting Materials:** ▪ List of all control tests performed on raw materials, with appropriate characterisation on starting materials. ▪ List of raw materials meeting compendia specifications. ▪ List of raw materials meeting in-house specifications including the tests performed and specifications ▪ Biological starting materials (human or animal origin) with information on the requirements to avoid risk of transmissible spongiform encephlopathies (TSEs) and human diseases (HIV, hepatitis,etc) in the final product including Certificate of Suitability (CEP). *Please refer Checklist A & B* **Reference:** WHO Guidelines on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical products (2010).
2.	**Intermediate Products (as appropriate):** ▪ List the routine tests performed and specifications for intermediates.
3.	**Finished Products (including diluents):** ▪ List routine tests performed and specifications for final product. ▪ Description of the method and retest criteria.
4.	**Analytical Validation Activities Performed:** ▪ Include complete description of the protocol used for each bioassay, the control standards, the validation of inherent variability of test and the establishment of acceptance limits for each assay.

D.	**STABILITY** (http://www.who.int/biologicals/publications/trs/areas/vaccines/stability/en/)
	▪ Information on stability of intermediates and final product, quality control methods and rationale for the choice of tests for determining stability. ▪ Information on the dates of manufacture of the lots, the lot numbers, the vial and dose size, and the scale of production. ▪ Describe the policy for assigning the date of manufacture of each component as well as the final product (e.g combination vaccine) and diluents, as appropriate. ▪ In addition to final product stability data at the recommended storage temperature, the accelerated stability data at elevated temperatures should be sufficient to justify the choice of Vaccine Vial Monitor (VVM) for use with the product [Vaccine Vial Monitor WHO/PQS/E06/IN05.1]
E.	**LOT SUMMARY PROTOCOL AND LOT RELEASE FOR VACCINE**
	▪ Lot Summary Protocol - a document which describes the key steps and critical test results at each step of the production process must be submitted. ▪ Lot release is a basic principle in the control of vaccine. The aim of lot release is the confirmation of consistency of production as each lot of vaccine is unique. ▪ Submit Lot/ Batch Release Certificate issued by the competent authority. ▪ Every batch of registered vaccines and plasma products imported is required to undergo physical testing for Lot Release activity. ▪ COVID-19 vaccine products imported and used during a pandemic are excluded from the requirement to conduct physical testing for Lot Release activity. ▪ Lot Release activity is implemented for biological products manufactured in Malaysia. **References:** - Guidelines for Independent Lot Release of Vaccines by Regulatory Authorities World Health Organization 2010 - Directive No. 16, 2014. *Bil. (23) dlm.BPFK/PPP/07/25 Direktif Untuk Pelaksanaan Vaccine Lot Release ke atas Semua Produk Vaksin Berdaftar di Malaysia* (14 January 2015) - Guidance Document for Biological Products Lot Release in Malaysia - Directive No. 9, 2020. *Bil. (9)dlm.BPFK/PPP/07/25Jld.4 Direktif Keperluan Menjalankan Ujian Fizikal Untuk Aktiviti Lot Release Bagi Semua Vaksin dan Produk Plasma Berdaftar Yang Diimport* (12 May 2020) - *Keputusan Pihak Berkuasa Kawalan Dadah (PBKD) Berkenaan Pengecualian Daripada Keperluan Menjalankan Ujian Fizikal Untuk Aktiviti Lot Release Bagi Semua Produk Vaksin COVID-19 Berdaftar Yang Diimport dan Digunakan Semasa Situasi Pandemik, NPRA.600-1/9/7(41)* (19 February 2021) - Directive No. 13, 2021. *NPRA.600-1/9/13(23) Direktif Berkenaan Pelaksanaan Aktiviti Lot Release Ke Atas Produk Vaksin dan Produk Plasma Yang Dikilangkan Di Malaysia* (28 April 2021)

F.	NONCLINICAL STUDIES FOR VACCINE
	▪ Vaccines are a diverse class of biological products and their nonclinical testing programs will depend on product-specific features and clinical indications. ▪ Preclinical testing is a prerequisite to moving a candidate vaccine from the laboratory to the clinic and includes all aspects of testing, product charaterization, proof of concept/ immunogenicity studies and safety testing in animals conducted prior to clinical testing in humans. ▪ Some live attenuated vaccines must be tested for safety in animals before they are used in humans. **References:** - WHO TRS 927 (2005) Annex 1: WHO guidelines on nonclinical evaluation of vaccines - WHO TRS 987 (2014), Annex 2: Guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines
G.	**CLINICAL STUDIES FOR VACCINE**
	▪ Clinical studies designed and conducted to meet WHO and international GCP principles. ▪ Tabulated summary of the clinical development program of the vaccine, in which critical parameters that may have changed during the clinical development. ▪ Copies of publications about these trials should accompany the submission. ▪ Clinical summary: Provide detailed summary and intepretation of the safety and efficacy data obtained from clinical studies that supports the current prescribing information. ▪ Clinical Expert Report: Provide an independent clinical expert report on the clinical studies (evidence of expertise and independence should be provided) **References:** - WHO TRS 924 (2004) Annex 1: WHO guidelines on clinical evaluation of vaccines:Regulatory expectations. - WHO TRS 850 (1995) Annex 3: Guidelines for Good Clinical Practice (GCP) for trials on pharmaceutical products.
H.	**POST MARKETING SURVEILLANCE FOR VACCINES**
	▪ Provide an outline of the post marketing pharmacovigilance plan for the vaccine. ▪ Periodic Benefit-Risk Evaluation Report (PBRER) in accordance to ICH Guideline E2C(R2) Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs. ▪ In the case of vaccines that have recently been registered/ licensed, provide information on any ongoing phase IV studies or on any active monitoring of the safety profile that is taking place including adverse events following immunization(AEFI). ▪ Risk management plan. Please also refer to Malaysian Guidelines on Good Pharmacovigilance Practices (GVP) for Product Registration Holders, First Edition, August 2021.

2.1.2 Biotechnology Products

(i) Definition

Biotechnological products includes the use of the new genetic tools of recombinant DNA to make new genetically modified organisms or genetic engineering products.

Products of recombinant technology are produced by genetic modification in which DNA coding for the required product is introduced, usually by means of a plasmid or viral vector into a suitable microorganism or cell line, in which DNA is expressed and translated into protein. The desired product is then recovered by extraction and purification.

(ii) Additional Requirements for Registration of Biotechnology Products

I.	PRODUCTION PROCESSES
	▪ The production system shall be well defined and documented. ▪ The effectiveness of the overall purification process for active substance shall be demonstrated. ▪ Validation of procedures for removing contaminating cellular DNA, viruses and impurities.
J.	**HOST CELL AND GENE CONSTRUCT**
	▪ Source of host cells, characterisation, stability, purity and selection. ▪ Information on gene construct, amino acid sequence, vector information and genetic markers for characterisation of production cells. ▪ Cloning process to form the final gene construct and mapping of sited used in constructions of final recombinant gene construct. ▪ Method of gene construct amplication and selection of recombinant cell.
K.	**SPECIFICATIONS**
	▪ Drug substances should include assays for identity, purity, potency, physiochemical and stability. ▪ Identity and quantity of impurities along with analytical data which supports impurities profile ▪ Acceptable limits of impurities and should be included in the specifications if present in finished products.

L.	**CHARACTERISATION**
	▪ Analytical testing performed to characterise the drug substance with respect to identity, purity, potency, and stability. ▪ Characterisation of drug substance include physiochemical characterisation, immunological properties and biological activity. ▪ Sufficient sequence information to characterise the product should be obtained. ▪ Post translational modifications should be identified and adequetly characterised, especially when such modifications are likely to differ from those found in natural counterpart and may influence biological, pharmacological and immunological properties of the product.
M.	**NONCLINICAL STUDIES**
	▪ Preclinical testing is a prerequisite to moving a candidate biotechnology products from the laboratory to the clinic and includes all aspects of testing, product charaterization, proof of concept/ immunogenicity studies and safety testing in animals conducted prior to clinical testing in humans. ▪ The primary goals of nonclinical studies/preclinical safety evaluation are to identify an initial safe dose and subsequent dose escalation schemes in humans, potential target organs for toxicity (whether such toxicity is reversible) and safety parameters for clinical monitoring **Reference**: ICH Topic S6 (R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.
N.	**CLINICAL STUDIES**
	▪ Clinical studies designed and conducted to meet WHO and international GCP principles. ▪ Overall approach to the clinical developement of a medicinal product. ▪ Overview of the clinical findings and provide an evaluation of benefits and risks based upon the conclusions of the relevant clinical studies. ▪ Interpretation of how the efficacy and safety findings support the proposed dose and target indication.

O.	POST MARKETING SURVEILLANCE FOR BIOTECHNOLOGY PRODUCT
	▪ Provide an outline of the post marketing pharmacovigilance plan. ▪ Periodic Benefit-Risk Evaluation Report (PBRER) in accordance to ICH Guideline E2C(R2) Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs. ▪ All relevant clinical and nonclinical safety data should cover the period of the report with exception of updates of regulatory authority or product registration holder (PRH) actions taken for safety reasons, as well as data on serious, unlisted adverse drug reactions (ADRs), which should be cumulative. ▪ Risk management plan

2.1.3 References for Vaccines and Biotechnology Products

Vaccines:

WHO (*http://www.who.int/biologicals/vaccines*)
WHO Technical Report Series: Vaccines

Biotechnology Products:

WHO

i) WHO Technical Report Series 1991 No. 814, Annex 3. Guidelines for assuring the quality of pharmaceutical and biological products prepared by recombinant DNA technology. *(under revision)*
ii) WHO Technical Report Series 1992 No 822, Annex 3. Guidelines for assuring the quality of monoclonal antibodies for use in humans.
iii) WHO Technical Report Series No 878, Annex 1 and Addendum. Requirements for the use of animal cells as in vitro substrates for the production of biologicals.
iv) WHO Technical Report Series No.786, Annex 3. Requirements for human interferons prepared from lymphoblastoid cells (Requirements for biological substances N0.42)
v) WHO Technical Report Series No.771, Annex 7 Requirements for human interferons made by recombinant DNA techniques (Requirement for biological substance No. 41)

EMA

i) EMA/CHMP/BWP/532517/2008. Guideline on Development, Production, Characterisation and Specification for Monoclonal Antibodies and Related Products
ii) CPMP/BWP/328/99. Development Pharmaceutics for Biotechnological and Biological Products - Annex to Note for Guidance on Development Pharmaceutics.
iii) EMEA/410/01 Rev. 3 Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products.

ICH

i) ICH Topic Q5A (R1) Quality of Biotechnological Products: Viral Safety Evaluation Of Biotechnology Products Derived From Cell Lines Of Human Or Animal Origin.

ii) ICH Topic Q5B Quality of Biotechnological Products: Analysis of the Expression Construct in Cell Lines Used for Production of r-DNA derived Protein Products.

iii) ICH Topic Q5D Quality of Biotechnological Products: Derivation and Characterisation of Cell Substrates used for Production of Biotechnological/ Biological Products.

iv) ICH Topic Q5C Quality of Biotechnological products: Stability Testing of Biotechnological/ Biological Products.

v) ICH Topic Q5D Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/ Biological Products.

vi) ICH Topic Q5E Biotechnological/ Biological Products Subject to Changes in Their Manufacturing Process: Comparability of Biotechnological/ Biological Products.

vii) ICH Topic Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products.

viii) ICH Topic Q2 (R1) Validation of Analytical Procedures: Text and Methodology.

ix) ICH Topic Q8 (R2) Pharmaceutical Development.

x) ICH Topic Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/ Biological Entities).

xi) ICH Topic S6 (R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.

2.2 REQUIREMENTS FOR REGISTRATION OF BLOOD PRODUCTS

2.2.1 Definition of Blood Product

Any therapeutic product derived from human blood or plasma and produced by a manufacturing process that pools multiple units.

Plasma-derived therapies and their recombinant analogs are unique among pharmaceuticals and biologics. Their production begins with a biological starting material, human plasma. Each therapy has a unique biochemical profile as a result of differences in production and processing methods that can lead to differing clinical responses and efficacy among patients.

Hence, from the starting material, through manufacturing and final distribution to patients, the complexities of producing blood products places it in a unique class of biologics.

Blood products are regulated as medicinal product. Blood products are inherently variable due to their biological nature, and the biological methods to test them. They are subjected to comprehensive assessment of the quality, efficacy and safety.

Four (4) principal complementary approaches are adopted:

- **Starting material:** Assurance of the quality and safety of the plasma for fractionation.
- **Manufacturing technique:** Control of the fractionation and subsequent manufacturing procedures for isolation, purification, viral inactivation and/or removal steps.
- **Good manufacturing practice (GMP):** Strict adherence to GMP. Adoption of GMP as an essential tool of Quality Assurance System.
- **Product Compliance:** Standardization of biological methods needed in characterisation of in-process and finished products.

Plasma for fractionation and blood products that are regulated by NPRA includes:

- Plasma products derived from plasma collected and fractionated in Malaysia for use in Malaysia;
- Plasma products derived from plasma collected and fractionated overseas for use in Malaysia; and
- Plasma products derived from overseas-sourced plasma fractionated in Malaysia for use overseas.

Note: *This document is applicable to all plasma-derived products containing an active and inactive ingredient that is derived from human blood.*

2.2.2 Requirements for Registration of Blood Products

1.	QUALITY OF PLASMA SOURCE MATERIAL
	Plasma Master File (PMF). It can also be a stand-alone document. Document pertaining to the collection and controls of source materials. Key elements of PMF are: ▪ Requirements for a formal contract governing purchase and supply of plasma. ▪ Source plasma. ▪ GMP status of the blood establishments/ collection centers. ▪ Description of the quality assurance system applying to plasma supply and use. ▪ Arrangements for donor selection, selection/exclusion criteria. ▪ Data on population epidemiology and blood-borne infections. ▪ Requirements for testing of samples of donations and pools. Mandatory serology on all plasma donations. Each unit of source material tested for HBsAg, anti-HIV and anti-HCV ▪ Plasma bags, plasma quality and plasma specifications. ▪ Arrangement for communication and review of post-donation information. ▪ Plasma inventory hold. ▪ Traceability from donor to end product and *vice versa.* **References:** - CHMP/BWP/3794/03 Rev. 1 Guideline on the Scientific Data Requirements for a Plasma Master File (PMF) - Checklist of Plasma Master File for Blood Products.
2.	**MANUFACTURING PROCESS AND CONTROL**
	Documents that verify each batch of source material intended for manufacture has been serological tested for hepatitis B (HBV), hepatitis C (HCV) and HIV. Each batch of source material must also be tested for HCV RNA by Nucleic Acid Testing (NAT) and (increasingly for other viruses including HIV, HBV, B19, and HAV) and exclusion of reactive donations. **Characterization:** Physicochemical and biological characterization: Specific tests that will provide information regarding identity, purity, potency, stability and consistency of manufacture for the drug substance. **Manufacture and Controls:** **i) Formula:** ▪ Include a list of all starting materials, reagents, monoclonal antibodies, intermediate products and auxiliary materials (buffers, sera, antibiotics etc.) with specifications or statement of quality for each. ▪ Excipients: List of excipients. ▪ For non-compendial excipients: Describe tests and specifications.

	▪ For novel excipients: Include description for preparation, characterisation and controls. ▪ When used as excipient in the product, the expiry date of the plasma-derived product should not be earlier than that of the finished product. **ii) Manufacturing:** ▪ Detailed description of manufacturing process and controls to demonstrate proper quality control or prevention of possible contamination with adventitious agents. ▪ In-process and final controls. - Viral inactivation and/ or removal processes - Viral validation studies and report - Pathogen safety document inclusive of Transmissible Spongiform Encephalopathies (TSEs) risk assessment - Information or certification supporting the freedom of reagents, inactive ingredients of human or animal origin from adventitious agents. - Process consistency - Analytical validation studies - Process validation studies (purification, sterility etc.) - Batch record and batch release specifications
3.	**THE FINAL PRODUCT**
	▪ Finished product testing and quality control ▪ Stability study program and expiration date ▪ Product history ▪ Container closure system, storage and handling ▪ Package insert and labels ▪ Lot/ batch release protocols ▪ Certificate of batch review and release from a competent authority
4.	**CLINICAL STUDIES**
	▪ Demonstrating product's efficacy
5.	**POST MARKETING SURVEILLANCE – mandatory follow-up**
	▪ Periodic Benefit-Risk Evaluation Report (PBRER) Risk Management Plans

2.2.3 Checklist of Plasma Master File for Blood Products

Section	Documents	Yes/No
1.	**General Information**	
1.1	Plasma Derived Products' List	
1.2	Overall Safety Strategy • Collection of plasma • Testing • Storage	
1.3	General Logistics • Flowchart of supply chain of plasma	
2.	**Technical Information on Starting Materials/Plasma**	
2.1	Plasma Origin • Information on Collection Centers • Information on Testing Centers • Selection/ Exclusion Criteria for Donors • Traceability	
2.2	Plasma Quality and Safety • Compliance with Ph. Eur. Monographs or relevant monographs • Screening Tests for Markers of Infection • Technical Characteristics of Bags and Bottles for Blood and Plasma Collection, Including Information on Anticoagulant Solutions Used • Storage and Transport • Procedures for any Inventory Hold Period • Characterisation of the Fractionation Pool	
2.3	Contract Between Manufacturer and Blood Collection Establishment(s) • System in place between the manufacturer and/or plasma fractionators/ processor on one hand, and blood collection establishments on the other hand which defines the conditions of their interaction and their agreed specifications	

2.2.4 References for Blood Products

The National Pharmaceutical Regulatory Division's requirements for registration of blood products are aligned with the scientific guidelines and recommendations for quality, clinical efficacy and safety and non-clinical of the World Health Organization (WHO), European Medicines Agency and International Conference of Harmonization (ICH).

Where appropriate, the relevant WHO, EMA and ICH guidelines on blood products shall be consulted in particular the followings:

WHO (*https://www.who.int/health-topics/blood-products-*)

i) WHO Technical report Series 941, Annex 4, Recommendations for production, control and regulation of human plasma for fractionation.
ii) WHO Technical report Series 924, Annex 4, Guidelines on viral inactivation and removal procedures intended to assure the viral safety of human plasma products.
iii) WHO Guidelines on tissue infectivity distribution in Transmissible Spongiform Encephalopathies.

EMA *(http://www.ema.europa.eu)*

i) EMA/CHMP/BWP/706271/2010 Committee for medicinal products for human use (CHMP) Guideline on plasma-derived medicinal products
ii) CHMP/BWP/3794/03 Rev. 1 Guideline on the Scientific Data Requirements for Plasma Master File (PMF)
iii) CPMP/BWP/268/95 Note for Guidance on Virus Validation Studies: The Design, Contribution and Interpretation of Studies Validating the Inactivation and Removal of Viruses
iv) EMEA/410/01 Rev. 3 Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products
v) EMA/CHMP/BPWP/144533/2009 rev. 2 Guideline on the Clinical Investigation of Recombinant and Human Plasma-Derived Factor VIII Products
vi) EMA/CHMP/BPWP/144552/2009 Rev. 1, Corr. 1* Guideline on Clinical Investigation of Recombinant And Human Plasma-Derived Factor IX Products
vii) EMA/CHMP/BPWP/94033/2007 rev. 2 Guideline on the Clinical Investigation of Human Normal Immunoglobulin for Intravenous Administration (IVIg)

ICH (*http://www.ich.org*)

i) ICH Topic 5QC Quality of Biotechnological products: Stability Testing of Biotechnological/ Biological Products.

3. CHECKLISTS

3.1 CHECKLIST A

Products Containing Animal-Derived Materials **WITH** a valid TSE risk evaluation Certificate of Suitability (CEP)

No.	Documents	Yes/ No
1.	TSE Risk Evaluation Certificate of Suitability (CEP)	
2.	Basic information providing a brief description of the following:	
3.	Rationale for using animal-derived materials	
4.	Source of Animals • Declaration of materials of porcine origin • Declaration of materials of other animal origin	
5.	Declaration of the nature of the animal tissue/ parts of animal used.	
6.	Description of the tissue/ organ-collection procedures and measures in place to avoid cross-contamination.	
7.	Nature and quantity of each animal-derived material used: • As a drug substance. • As an excipient or adjuvant. • As a starting material used in the manufacture of a drug substance. • As a starting material used in the manufacture of excipient. • As a reagent or culture media component used in manufacture. • As a reagent or culture media component used in establishing master cell banks. • As a reagent or culture media component used in establishing working cell banks. • Others, please provide details.	
8.	Declaration that the final product does not contain any animal-containing materials with the relevant evidence (if applicable).	
9.	Other supporting documents e.g. *Halal* Certification of the animal derived ingredient from a competent *Halal* Certification Authority.	
10.	Labelling of the animal derived materials.	

3.2 CHECKLIST B

Products Containing Animal-Derived Materials **WITHOUT** a valid TSE risk evaluation Certificate of Suitability (CEP)

Section	Documents	Yes/ No
1.	Detailed Assessment Report for the risk of TSE. The scope of this assessment report should include the following:	
2.	Rationale for using animal-derived materials	
3.	Source of Animals • Declaration of materials of porcine origin • Declaration of materials of other animal origin	
4.	Declaration of the nature of the animal tissue/ parts used.	
5.	Description of the tissue/ organ-collection procedures and measure in place to avoid cross-contamination.	
6.	Detail of the risk factors associated with the route of administration and maximum therapeutic dosage of the product.	
7.	Nature and quantity of each animal-derived material used: • As a drug substance • As an excipient or adjuvant • As a starting material used in the manufacture of a drug substance. • As a starting material used in the manufacture of excipient. • As a reagent or culture media component used in manufacture. • As a reagent or culture media component used in establishing master cell banks. • As a reagent or culture media component used in establishing working cell banks. • Others, please provide details.	
8.	Relevant information to support the claim that the manufacturing process is capable of inactivating TSE agents.	
9.	Certificates of analysis for each animal-derived materials used.	
10.	Declaration that the final product does not contain any animal-containing materials with the relevant evidence (if applicable)	
11.	Other supporting documents e.g. Halal Certification of the animal derived ingredient from a competent Halal Certification Authority.	
12.	Labelling of the animal derived materials.	

APPENDIX 5

GUIDELINE ON REGISTRATION OF GENERICS

IMPORTANT NOTES:

This document shall be read in conjunction with the relevant sections of the main guidance document: **Drug Registration Guidance Document (DRGD)**, which is in accordance to the legal requirements of the **Sale of Drugs Act 1952** and the **Control of Drugs and Cosmetics Regulations 1984**.

1. DEFINITION

A generic product is a product that is essentially similar to a currently registered product in Malaysia. However, the term generic is not applicable to Biologics.

2. GENERIC APPLICATION

The following categories of product can be processed as generic application provided that it fulfils the definition of a generic product.

(i) **Scheduled Poison**

(Known as Controlled Medicine/ Controlled Poison)

Products containing active ingredients as listed in the First Schedule under Poisons Act 1952.

(ii) **Non-Scheduled Poison**

(Known as "Over-the-Counter", OTC)

Products containing active ingredients which are not listed in the First Schedule under Poisons Act 1952; and are excluding active ingredients which are categorized under health supplements or natural products or cosmetics.

(a) **Full Evaluation**

Other than listed at (b) Abridge Evaluation

(b) **Abridged Evaluation**

which include, but not limited to the following:

- Antiseptics/ skin disinfectants;
- Locally-acting lozenges/ pastilles;
- Topical analgesic/ counter-irritants;
- Topical nasal decongestants;
- Emollient/ demulcent/ skin protectants;
- Keratolytics;
- Anti-dandruff;
- Oral care;
- Anti-acne;
- Medicated plasters/ patch/ pad; and
- Topical antibacterial.

For medicinal gases classified as generic products, please refer to Directive No. 8, 2021 and Guideline on Registration of Medicinal Gases.

Reference:

- Directive No. 8, 2021, NPRA.600-1/9/13 (18): *Direktif Berkenaan Pengukuhan Pelaksanaan Kawalan Regulatori Ke Atas Produk-Produk Gas Perubatan dan Penggunaan Guideline on Registration of Medicinal Gases* (11 February 2021)

3. SUBMISSION OF APPLICATION

Applicants are advised to refer to **Section A (5. Application Procedures)** of the DRGD for further explanation.

4. EVALUATION TIMELINE FOR GENERIC APPLICATION

Table 1: Evaluation Timeline for Generic Application

No.	Product Category	Evaluation Timeline
(A)	**Full Evaluation**	
	Generic (Schedule Poison)	**210 working days**
	Generic (Non-Schedule Poison)	**210 working days**
(B)	**Abridged Evaluation**	
	Generic (Non-Schedule Poison) (i) Single active ingredient (ii) Two (2) or more active ingredients	 **116 working days** **136 working days**

5. REQUIREMENTS FOR GENERIC APPLICATION

Please refer to the following Appendices supplemented together with the DRGD for further information, where applicable:

Appendix 9	Fees
Appendix 11	Regulatory Control of Active Pharmaceutical Ingredients (APIs)
Appendix 12	Priority Review
Appendix 13	Designation and Registration of Orphan Medicines
Appendix 14	Evaluation Routes
Appendix 15	Requirements for Full Evaluation and Abridged Evaluation
Appendix 16	Bioequivalence (BE) Requirements
Appendix 17	Product Names Not Permitted To Be Registered
Appendix 18	List of Permitted, Prohibited and Restricted Substances
Appendix 19	General Labelling Requirements
Appendix 19A	Prohibited Visual/ Graphics/ Statements on Label
Appendix 20	Specific Labelling Requirements
Appendix 21	Special Conditions for Registration of a Particular Product or Group of Products

Appendix 22	Educational Materials
Appendix 23	Patient Dispensing Pack for Pharmaceutical Products
Appendix 24	Appeal
Appendix 25	Guideline for the Submission of Protocol of Analysis (POA)
Appendix 26	Guideline for the Submission of Analytical Method Validation (AMV) Documents
Appendix 27	Inspection
Appendix 33	Explanatory Notes for Repackers

6. REFERENCES FOR GENERIC APPLICATION

Applicants are also advised to refer to NPRA's website for the latest registration requirements. In addition, other relevant and latest international guidelines e.g. by EMA, USFDA and ICH should also be referred to complement the ASEAN Guidelines and the DRGD as appropriate.

7. OTHERS

Classification of Products containing Glucosamine, Chondroitin and Methylsulphonylmethane (MSM)

<table>
<tr><th>No.</th><th colspan="2">Product</th><th>Product Category</th><th>Route of Evaluation</th><th>Condition on Product Indication</th><th>Remark</th></tr>
<tr><td rowspan="2">1.</td><td rowspan="2">Products containing Glucosamine</td><td>As single active ingredient</td><td>OTC</td><td>Full evaluation</td><td>As adjuvant therapy for osteoarthritis</td><td rowspan="2">Products containing glucosamine in combination with other health supplement ingredients are only allowed to be registered for therapeutic purposes and NOT allowed to be registered as Health Supplement Product.</td></tr>
<tr><td>As combination with Chondroitin and/ or MSM</td><td>OTC</td><td>Full evaluation</td><td>As adjuvant therapy for osteoarthritis</td></tr>
</table>

No.	Product		Product Category	Route of Evaluation	Condition on Product Indication	Remark
2.	Products containing Chondroitin	As single ingredient OR In combination with other supplement ingredients	Health supplement	Abridged Evaluation	No therapeutic claims are allowed	-
3.	Products containing MSM	As single ingredient OR In combination with other supplement ingredients	Health supplement	Abridged Evaluation	No therapeutic claims are allowed	-
		As combination with Chondroitin	Health supplement	Abridged Evaluation	No therapeutic claims are allowed	-

References: Circulars

(i) *Bil. (66) dlm BPFK/02/5/1.3*
Produk yang Mengandungi Glucosamine dan Chondroitin (14 November 2006)

(ii) *Bil. (20) dlm.BPFK/PPP/01/03*
Produk yang mengandungi Glucosamine, Chondroitin dan Methylsulfonylmethane (MSM) (31 December 2008)

APPENDIX 6

GUIDELINE ON REGISTRATION OF HEALTH SUPPLEMENTS

IMPORTANT NOTES:

This guideline will serve as an additional reference guide for the registration of health supplement products, which consist of pharmaceutical active ingredients for human use as well as ingredients derived from natural sources.

Applicants are advised to refer to main **Drug Registration Guidance Document** for the common requirements for the preparation of a well-structured dossier application to be submitted for product registration.

Contents:

1. Definition
- 1.1 Health Supplement (HS)
- 1.2 Indication
- 1.3 Route of Administration
- 1.4 Exclusion from Health Supplement
- 1.5 Exemption

2. Active Ingredients

3. Maximum Daily Levels of Vitamins and Minerals for Adults Allowed in Health Supplements

4. Health Supplement Claims
- 4.1 Conditions
- 4.2 Types and Evidence of Claims
- 4.3 Claims Substantiation
- 4.4 Illustrative Substantiation Evidence

5. Specific Dossier Requirement for Registration of Health Supplements
Product validation
- 5.1 Product Name
  - 5.1.1 List of Non-Permissible Product Name for Health Supplement Products
- 5.2 Dosage Forms
- 5.3 Active Ingredients
  - 5.3.1 Name of Active Ingredient
  - 5.3.2 Strength of active ingredient
  - 5.3.3 Source of Active ingredient
  - 5.3.4 Remarks on active ingredient (if any)
  - 5.3.5 Use of Protected/ Endangered Ingredients

5.3.6 Additional data to support new health supplement active ingredients

5.4 Any Animal Origin
5.5 Manufacturer
5.6 Contract Manufacturer
5.7 Second Source Information
5.8 Other Manufacturer
5.9 Imported Products
5.10 Product Containing Premix
5.11 Replacement Product

Administrative Data and Product Information
SECTION A: PRODUCT PARTICULARS

5.12 Product Description
5.13 Indication/ Usage
5.14 Recommended Dose (Dose/ Use Instruction) & Route of administration
5.15 Contraindication
5.16 Warnings and Precautions
5.17 Drug Interactions
5.18 Pregnancy and Lactation
5.19 Side Effects/ Adverse Reactions
5.20 Signs and Symptoms of Overdose and Treatment
5.21 Storage Conditions
5.22 Shelf Life
5.23 Therapeutic Code (If any)

SECTION B: PRODUCT FORMULA
5.24 Batch Manufacturing Formula (BMF)

SECTION C: PARTICULARS OF PACKING
5.25 Packaging

SECTION D: LABELLING REQUIREMENTS
5.26 Product label
5.27 Standard Labelling for Health Supplements
5.28 Prohibited Visual/ Graphics on Label
5.29 Package insert (Optional)

SECTION E
5.30 Product Owner
5.31 Letter of authorization from product owner
5.32 Letter of appointment of contract manufacturer and/ or repacker
5.33 Letter of acceptance as contract manufacturer and/ or repacker
5.34 Certificate of Pharmaceutical Product (CPP), Certificate of Free Sales (CFS) and Good Manufacturing Practice (GMP)
5.35 GMP/ CFS Template

5.36 Attachment of Protocol Analysis

SECTION P: DRUG PRODUCT

5.37 Manufacturing process

5.38 Control of Critical Steps and Intermediate/In Process Quality Control (IPQC)

5.39 Finished Product Quality Control

- Quality Control Test For Health Supplement Product
- Certificate of Analysis of Finished Product

5.40 Stability Data

SECTION S: DRUG SUBSTANCE

5.41 Specifications and Certificate of Analysis of Active Ingredient

Attachment 1: **Checklist: Dossier Requirement for Health Supplements**

Attachment 2: **Table 17: Allowable Claims for Specific Active Ingredients in Health Supplements**

1. DEFINITION

1.1 HEALTH SUPPLEMENT (HS)

Health Supplement (HS) refers to any product used to supplement a diet and to maintain, enhance and improve the health function of human body. It is presented in small unit dosage forms (to be administered) such as capsules, tablets, powder, liquids and shall not include any sterile preparations (i.e. injectable, eye drops). It may contain one or more, or the following combinations:

i) Vitamins, minerals, amino acids, fatty acids, enzymes, probiotics, and other bioactive substances;
ii) Substances derived from *natural sources, including animal, mineral and botanical materials in the forms of extracts, isolates, concentrates, metabolite;
iii) Synthetic sources of ingredients mentioned in (i) and (ii) may only be used where the safety of these has been proven.

1.2 INDICATIONS

i) Used as a Health Supplement;
ii) Vitamin and mineral supplements for pregnant and lactating women.

1.3 ROUTE OF ADMINISTRATION

Oral

1.4 EXCLUSION FROM HEALTH SUPPLEMENTS:

Health Supplements shall NOT include:

i) Any product as a sole item of a meal;
ii) Any injectable and sterile preparation;
iii) Any cells, tissues, organs or any substance derived from the human body;
iv) Any substance listed in the Schedule of the Poison Act;
v) Any other route of administration other than the oral route.

1.5 EXEMPTION FOR REGISTRATION

Extemporaneous preparations prepared and given directly to the patient by a healthcare practitioner during the course of treatment are exempted.

2. ACTIVE INGREDIENTS

Listed active ingredients can be checked at the NPRA website https://www.npra.gov.my/ using Product Search.

Classification of products containing Glucosamine, Chondroitin and Methylsulphonylmethane (MSM)

No.	Product		Product Category	Route of Evaluation	Condition on Product Indication	Remark
1.	Products containing Glucosamine	As single active ingredient	OTC	Full evaluation	As adjuvant therapy for osteoarthritis	Products containing glucosamine in combination with other health supplement ingredients are only allowed to be registered for therapeutic purposes and NOT allowed to be registered as Health Supplement Product.
		As combination with Chondroitin and/ or MSM	OTC	Full evaluation	As adjuvant therapy for osteoarthritis	
2.	Products containing Chondroitin	As single ingredient OR In combination with other supplement ingredients	Health supplement	Abridged Evaluation	No therapeutic claims are allowed	-
3.	Products containing MSM	As single ingredient OR In combination	Health supplement	Abridged Evaluation	No therapeutic claims are allowed	-

No.	Product		Product Category	Route of Evaluation	Condition on Product Indication	Remark
		with other supplement ingredients				
		As combination with Chondroitin	Health supplement	Abridged Evaluation	No therapeutic claims are allowed	-

References: Circulars

(i) *Bil (66) dlm BPFK/02/5/1.3*
Produk yang Mengandungi Glucosamine dan Chondroitin (14 November 2006)

(ii) *Bil. (20) dlm.BPFK/PPP/01/03*
Produk yang mengandungi Glucosamine, Chondroitin dan Methylsulfonylmethane (MSM) (31 December 2008)

3. MAXIMUM DAILY LEVELS OF VITAMINS AND MINERALS FOR ADULTS ALLOWED IN HEALTH SUPPLEMENTS

NO.	VITAMINS & MINERALS	UPPER DAILY LIMIT
1.	Vitamin A	5000 IU
2.	Vitamin D	1000 IU
3.	Vitamin E	800 IU
4.	Vitamin K (K1 and K2) [1]	0.12mg
5.	Vitamin B1 (Thiamine)	100 mg
6.	Vitamin B2 (Riboflavine)	40 mg
7.	Vitamin B5 (Panthothenic Acid)	200 mg
8.	Vitamin B6 (Pyridoxine)	100 mg
9.	Vitamin B12 (Cyanocobalamin)	0.6 mg
10.	Vitamin C (Ascorbic Acid)	1000 mg
11.	Folic Acid	0.9 mg
12.	Nicotinic Acid	15 mg
13.	Niacinamide (Nicotinamide)	450 mg
14.	Biotin	0.9 mg

NO.	VITAMINS & MINERALS	UPPER DAILY LIMIT
15.	Boron	6.4 mg
16.	Calcium	1200 mg
17.	Chromium	0.5 mg
18.	Copper	2 mg
19.	Iodine	0.3 mg
20.	Iron [2]	20 mg
21.	Magnesium	350 mg
22.	Manganese	3.5 mg
23.	Molybdenum	0.36 mg
24.	Phosphorus	800 mg
25.	Selenium	0.2 mg
26.	Zinc	15 mg

Note:

1. *Vitamin K (K1 and K2) is restricted only for combination with other vitamins and minerals in oral preparations. Vitamin K (K1 and K2) as a single ingredient in an oral preparation is not allowed.*
2. *For pre and antenatal use, as part of a multivitamin and mineral preparation, levels higher than the 20mg limit established for adults may be permitted at the discretion of the Authority.*
3. *Any form of fluoride as an ingredient is not permitted in formulation of health supplement products.*

4. HEALTH SUPPLEMENT CLAIMS

4.1 CONDITIONS

All claims made for health supplements (HS) shall:

i) be consistent with the definition of HS;
ii) enable consumers to make an informed choice regarding products;
iii) not be misleading or false;
iv) support the safe, beneficial and appropriate use of the product;
v) maintain the level of scientific evidence proportional to the type of claims;
vi) be for health maintenance and promotion purpose only;

vii) not be medicinal or therapeutic in nature, such as implied for treatment, cure or prevention of disease.

4.2 TYPES AND EVIDENCE OF CLAIMS

A health supplement claim refers to the beneficial effects of consuming HS to promote good health and well-being (physical and mental) by providing nutrition, enhancing body structure/ function, relieving physiological discomfort and/or reducing the risk of health related conditions or diseases.

Types of HS claims are:

- General or Nutritional Claims (*Table 1*);
- Functional Claims (medium) (*Table 2*);
- Disease Risk Reduction Claims (high) (*Table 3*).

For a HS product making a General or Functional Claim on vitamin(s) and/or mineral(s), it must contain a minimum of 15% of the Codex Nutrient Reference Value (NRV) per daily dose of the vitamin(s) and/or mineral(s). Other ingredients must be substantiated by supporting evidence.

For example, if the vitamin content is less than 15% NRV, the specific claim for this vitamin is not allowed unless there is evidence to support the claimed effect below this value.

For a HS product with Disease Risk Reduction Claim, it must be substantiated by supporting evidences.

Table 1: General or Nutritional Claims

Level of claim	Definition	Examples/ Wording of claim	Criteria	Evidence to substantiate HS claims
General or Nutritional Claims	▪ General Health Maintenance ▪ Benefits derived from supplementation beyond normal dietary intake	▪ Supports healthy growth and development ▪ Nourishes the body ▪ Relieves general tiredness, weakness ▪ Helps to maintain good health ▪ For energy and vitality ▪ For strengthening the body	▪ Is in line with established nutrition knowledge in reference texts ▪ Is related to general well-being in line with scientific knowledge ▪ Claim does not refer to the structure and/or function of the human body ▪ In accordance to HS principles and practice in Malaysia	**1 or more of the following evidences:** i) Standard reference e.g. reference textbooks, pharmacopoeia, monographs ii) Recommendations on usage from reference regulatory authorities or reference organisations

Please refer to 4.4 Illustrative Substantiation Evidence List for the list of acceptable references, organisations and authorities.

Table 2: Functional Claims (medium)

Claims must be adequately substantiated through ingredient-based evidence, and when necessary, through product-based evidence.

Types of HS claim	Definition	Examples/ Wording of claims	Criteria	Evidence to substantiate HS Claims
Functional Claims (medium)	▪ Maintains or enhances the structure or function of the human body, excluding disease-related claims	Acceptable claims based on the single ingredient e.g. ▪ Vitamin A helps to maintain growth, vision and tissue development ▪ Vitamin D helps in normal development and maintenance of bones and teeth. ▪ Chondroitin helps to promote healthy joints	For claims on established nutrients and ingredients such as vitamins & minerals with daily recommended values ▪ Meet the conditions for nutrient function claims as set by the Authority ▪ Claims have consistent scientific support according to scientific review and evaluation ▪ In accordance to HS principles and practice in Malaysia	**1 or more of the following evidence:** i) Standard reference e.g. reference textbooks, pharmacopoeia, monographs ii) Recommendations on usage from reference regulatory authorities or reference organisations iii) Good quality scientific evidence from human observational studies (refer to ASEAN Guidelines on efficacy data requirement) **(only in the event that human experimental study is not ethical, animal studies will be accepted together with epidemiological studies or other scientific literature and documented traditional use)** iv) Peer-reviewed scientific data or meta-analysis

Refer to 4.4 Illustrative Substantiation Evidence List for the list of acceptable references, organisations and authorities.

Table 3: Disease risk reduction (high)

Types of HS claim	Definition	Examples/ Wording of claims	Criteria	Evidence to substantiate HS Claims
Disease risk reduction	▪ Significantly altering or reducing a risk factor of a disease or health related condition.	▪ Helps to reduce risk of osteoporosis by strengthening bone ▪ Helps to reduce the risk of dyslipidaemia	▪ The relationship between the HS ingredient or product and disease risk reduction is supported by consistent scientific evidence ▪ Documented in authoritative reference texts ▪ Recognised by the Authority reference or international organisations or regulatory authorities ▪ Adheres to the key principles of HS claims	**Compulsory evidence:** i) Scientific evidence from human intervention study on ingredient and/or product ii) Toxicological study (chronic) iii) Pharmacological study **At least 1 additional evidence:** i) Standard reference e.g. reference textbooks, pharmacopoeia, monographs etc. ii) Recommendations on usage from reference regulatory authorities or reference organisations iii) Evidence from published scientific reviews or meta-analysis iv) Report prepared by expert committees/ expert opinion (subject to the Authority approval)

Refer to 4.4 Illustrative Substantiation Evidence List for the list of acceptable references, organisations and authorities

4.3 CLAIMS SUBSTANTIATION

Claims must be in line with the respective HS principles and supported by adequate evidence. To reflect the all available usage evidence (including relevant scientific evidence), the evidence shall be summarized as part of the substantiation document for the claim presented in the **Table 4** below:

Note: *Evidence not summarised and presented in the above format will not be further evaluated*

Indication / claim	Product/ Ingredient studied	Dosage and administration route	Duration of treatment	Type of evidence (scientific evidence)	Study design	Study population	Summary of findings	Limitations of the study	Source of evidence i) Author ii) Title iii) Publication details iv) Year v) Type (text,…)

4.4 ILLUSTRATIVE SUSBSTANTIATION EVIDENCE LIST

Reference texts

a. Martindale, latest edition. The Complete Drug. Pharmaceutical Press, 2009.
b. The ABC Clinical Guide to Herbs. American Botanical Council
c. WHO Monographs on Selected Medicinal Plants
d. British Pharmacopoeia
e. United States Pharmacopoeia
f. Indian Pharmacopoeia
g. Chinese Pharmacopoeia
h. Natural Standards (*www.naturalstandard.com*)
i. Office of Dietary Supplements, National Institutes of Health - Dietary Supplement Fact Sheets (*https://ods.od.nih.gov/factsheets/list-all/*)

Organisations

a. American Botanical Council (*www.herbalgram.org*).
b. American Nutraceutical Association
c. CODEX Alimentarius
d. Global Information Hub for Integrated Medicine (*http://www.globinmed.com*)
e. National Centre for Complementary and Alternative Medicine (*http://nccam.nih.gov/*)
f. Office of Dietary Supplements, National Institutes of Health (USA) (*http://ods.od.nih.gov*)

Reference regulatory authorities

a. Australia TGA
b. Chinese Health Authority on Chinese medicinal herbs
c. European Commission
d. Health Canada
e. United States FDA

Notes:

1. *This list is not meant to be exhaustive and will be reviewed from time to time.*
2. *The Authority will conduct a detailed evaluation of the evidence included in the report to ensure that the health claim is substantiated.*
3. *The Authority will consider review other than those listed above, if the standards of evidence are consistent with those of the Authority.*
4. *All references must be current.*

5. SPECIFIC DOSSIER REQUIREMENT FOR REGISTRATION OF HEALTH SUPPLEMENTS

PRODUCT VALIDATION

5.1 Product Name

- The product name may include product name, dosage form and strength (e.g. XYZ Capsule 500mg)
- Dosage form and strength of product are required to be part of the product name to allow for multiple dosage forms (e.g. tablet, capsule) and strengths (e.g. 200mg and 400mg) for any particular named (proprietary or generic) product.
- If a registered product name is found to be similar to another registered product, NPRA reserves the rights to request for the change in the product name.
- Product with more than one (1) active ingredient should not include the strength of active ingredients in the product name.
- The product name may include the brand name or trademark name, if applicable.
- Any product name that is the same or similar either in writing or pronunciation, with the product name of an adulterated product is prohibited.

5.1.1 List of Non-Permissible Product Name for Health Supplement Products

No.	Issue	Example
1.	**Prohibited use of disease names as stated in the Medicines (Advertisement and Sale) Act 1956 (revised 1983)**	Diabetes, Asthma, Cancer
2.	**Prohibited use of a single active ingredient as a product name in products containing more than one active ingredient unless product name contains words such as 'Plus, Compound, Complex, Herbanika**	If the product contain Vitamin C, Vitamin E and Fish Oil Product name: "Vitamin C" is not allowed but product name: "Vitamin C Plus" is allowed.
3.	**Prohibited use of superlative** Names that indicates superiority or inefficacy	Power, Superior, Pure, Mustajab, Safe, Healthy, Penawar, VIP, Good, World Number 1

No.	Issue	Example
4.	**Prohibited use of spelling of words that may cause confusion** i) Words that involve names of/ part thereof: 20 disease names prohibited in the Medicines (Advertisement and Sale) Act 1956 (Revised 1983) ii) Other diseases without scientific proof iii) Prohibited indication	Go Out = GOUT (label) Utix
5.	**Prohibited use of names that may cause ambiguity** Ambiguous product name	B For Energy?
6.	**Prohibited use of names that may be offensive or indecent**	SENXBIG=SEnXBIG (label) Sexy, Enjoy, Paradise, Heavenly, Blue boy, Casanova, Desire
7.	**Product name not congruent with the active ingredient**	The active ingredient is Evening Primrose oil (EPO) and the product name: "Marine tablet" is not allowed
8.	**Prohibited use of product names that has elements of ludicrous belief** Statements referring to ancient beliefs/ negative spirits/ supernatural power	Words such as miracle, magic, magical, miraculous, saintly, heavenly
9.	**Prohibited use of product names similar to the existing approved product names** Product name similar to the spelling and pronunciation of words of existing product names	Elegen vs L-gen vs L-jen Forte vs Fort
10.	**Prohibited use of product names that may cause ambiguity in the nature of product (drug/ food/ beverage)** Product name similar to a food/ beverage name	Juice, Health drink, Beverage, Kooky

No.	Issue	Example
11.	**Prohibited use of product names that represents professional advice or opinion**	Dr Sunny, Professor
12.	**Product name that symbolizes a claim**	Vigour, Youthful, High, Hi
13.	**Product name that uses strength but formulation contains more than one active ingredient**	If the product contains multivitamins and minerals. Product name: "XXX multivitamins and minerals 500mg" is not allowed.
14.	**Other prohibited product names**	Minda, IQ, Smart, Unique, Ultra Mega, Detox, Defence, Immunity
15.	**Names of organs and brain**	Heart, kidney, skin, liver

Note:

1. *This list is not meant to be exhaustive and will be reviewed from time to time.*
2. *The Authority reserves the right to disallow any other words, phrases or graphics for product label, which in its opinion is misleading, improper or not factual.*

5.2 Dosage Forms

- Allowed dosage forms include:
  a) Tablets
     Caplet, lozenge, chewable tablet, dispersible tablet, effervescence tablet, uncoated tablet, enteric coated tablet, sugar coated tablet, film coated tablet, extended release tablet;
  b) Capsules
     Soft capsule, hard capsule, enteric coated capsule, chewable soft capsule, extended released capsule;
  c) Powder/ Granules
  d) Liquid
     Emulsion, syrup, spray, suspension.
- Products in the shape of animal dosage forms are not allowed.
- Supporting data from established references (e.g. Standard Pharmacopeia) shall be required for a new dosage form.
- The form that correctly describes it in terms of its product quality control specifications and performance shall be selected.
- A separate application for registration is required for each dosage form.
- The following documents are required during submission of product dossier for **sustained-release/ extended-release/ timed-release dosage form**
  i) Protocol of analysis;
  ii) In-Process Quality Control (IPQC);
  iii) Finished Product Specification (FPQC);
  iv) Certificate of Analysis (COA).

5.3 Active Ingredients

5.3.1 Name of Active Ingredient :

- Please select active ingredient from the search database. If the substance is not listed, please select the "Not Listed Ingredient" button. An automatic e-mail will be sent to NPRA for notification.
- Approved names and pharmacopoeia names of ingredients shall be used whenever possible.

5.3.2 Strength of active ingredient :

- To enter the content of active ingredients (numerical) and then select the weights and measures from the given list.

- Content of the ingredients shall be expressed accordingly in the following manner:
    a. quantity per unit dose (e.g. for unit dose formulations - tablet, capsule, lozenge, etc.)
    b. percentage composition (%w/w, %w/v, %v/v, etc.)
    c. weight per ml. (e.g. for solutions,suspension etc.)
    d. quantity (percentage or amount) per measured dose (e.g. oral liquids, drops, etc.)
- Metric weights and measures shall be used.

5.3.3 Source of Active ingredient:

To specify the source such as animal, plant, synthetic or others (to specify)

5.3.4 Remarks on active ingredient (if any):

- To specify the equivalent/providing amount of active component from the raw material (e.g: Sodium ascorbate 520 mg providing.... Vitamin C)
- Declaration of species name from natural source (plant, animal or others)

5.3.5 Use of Protected/ Endangered Ingredients

a) Protected/ Endangered Wildlife Species

It is the responsibility of the applicant to ensure that the ingredient(s) derived from wildlife species, its parts and derivatives used in the formulation **COMPLIES** with the Wildlife Conservation Act 2010 (Act 716) and International Trade in Endangered Species Act 2008 (Act 686). Both guidelines can be downloaded at the PERHILITAN website (*http://www.wildlife.gov.my*).

The applicant shall contact the following department to obtain the necessary permit/ license. A copy of the permit/ license shall be submitted with the application form for product registration.

Department of Wildlife and National Parks, Peninsular Malaysia
Km. 10, Jalan Cheras,
56100 Kuala Lumpur,
Tel: +603-90866800, Fax: +603-90753873

b) Endangered Botanical Species

It is the responsibility of the applicant to declare the source of the botanical ingredient if it is listed under the International Trade in Endangered Species Act 2008 (Act 686). If the ingredient is from a local source, a special permit/ license shall be obtained from the:

Division of Protection and Quarantine of Plants,
Department of Agriculture,
Tingkat 1-3, Wisma Tani,
Jalan Sultan Salahuddin,
50632 Kuala Lumpur.
Tel: +603 - 20301400, Fax: +603 - 26913550.

5.3.6: Additional data to support new health supplement active ingredients

No.	Types of documents	Checklist
1.	Standard/ established references	• Martindale, Pharmacopeias, Monograph etc.
2.	Information from the competent authorities of reference countries	• Information shall be provided from the competent authorities of reference countries (Refer to 9.6.5) • Example of supporting documents: ➢ Registration status and maximum registered dosage as health supplement ➢ established monograph ➢ GRAS status
3.	Clinical studies or scientific evidences	• Full published articles • Unpublished data may be considered • Mandatory for high claim
4.	Non-clinical studies to support long term-use	
5.	Toxicology studies with the determination of NOAEL (No observed adverse effect level)	
6.	Pharmacological study	
7.	Justification for the use of new active ingredient as health supplement	
8.	Registration status worldwide	• Registered and Marketed Date

Note: *The documentation must support the safety use and dose of new active ingredients as a health supplement.*

5.4 Any Animal Origin

Any source from animal origin must be declared and the type of animal must be specified.

5.5 Manufacturer

The requirements for Good Manufacturing Practice (GMP) for the manufacturers are in **Table 5** below:

Table 5:

Level of claims	Requirements for GMP
General/ Functional	a) Malaysia *Guidelines on Good Manufacturing Practice for Traditional Medicine and Health Supplement latest edition*. Or b) The accepted standards for GMP will be determined by the category the product is classified in the country of origin. For example, if the product is classified as food in the country of origin, GMP certificate of food standard issued by relevant country authority will be accepted on condition that the standards are similar to those practices in Malaysia. Or c) If the product is not regulated in the country of origin and does not require GMP certification, the manufacturer will have to produce a GMP certificate issued by an independent body recognised by the Authority. Information including the standard/ regulations/ legislation to which the inspection was based upon must be mentioned.
Disease Risk Reduction	a) Malaysia *Guidelines on Good Manufacturing Practice for Traditional Medicine and Health Supplement latest edition* Or b) The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) Standards. Or c) GMP certificates issued by relevant country authority will be accepted on condition that the standards are similar to PIC/S Standards

5.6 Contract Manufacturer

Contract manufacturer is applicable when the product owner is not the product manufacturer.

5.7 Second Source Information

An application for a second source may be considered when deemed necessary. This second source product shall be the same as the first product in all respects except for the site of manufacture.

5.8 Other Manufacturer

Any manufacturer involved in assembly, fill & finish, active ingredients, packing, labeling etc.

5.9 Imported Products

Imported product needs to be declared.

5.10 Product Containing Premix

Premixed active ingredient(s) is a combination of two or more active ingredients that are previously manufactured by a different manufacturer.

Certificate of GMP for manufacturer/ supplier is required for the premixed ingredient(s) in formulation. The requirements for GMP are same as in Table 5 as above.

5.11 Replacement Product

A PRH is not allowed to register/ hold two or more products with similar formulation (same active ingredient of raw material, strength and dosage form) at any one time, except for product variants.

A letter of justification for replacement by the PRH is required.

ADMINISTRATIVE DATA AND PRODUCT INFORMATION

SECTION A: PRODUCT PARTICULARS

5.12 Product Description

Beriefly state the **visual and physical characteristics** of the product, according to **Table 6** below (where applicable):

No.	Dosage Form	Description
1.	Tablet	Shape, size, colour, odour, taste, marking, emboss, type of tablet (e.g. coated, uncoated, film, sugar etc.)
2.	Capsule	Shape, size, colour, odour, taste, marking, emboss, coating, content of capsule, type of capsule (e.g.: soft, hard, chewable etc.)
3.	Liquid	Clarity, type (e.g. solution/ suspension/ emulsion etc.), taste, odour, colour.
4.	Powder	Colour, odour, taste etc.
5.	Pill	Colour, odour, taste, size etc.
6.	Granules	Colour, odour, taste, size etc.

5.13 Indication/ Usage

Briefly state the recommended use(s) of product. The following indications are allowed:

- Used as a Health Supplement; or
- Vitamins and mineral supplements for pregnant and lactating women.

5.14 Recommended Dose (Dose/ Use Instruction) & Route of administration

State the dose (normal dose, dose range) and dosing schedule (frequency, duration if applicable). Dosage for adults and children (where appropriate) shall be stated.

5.15 Contraindication

State conditions for which or under which the product shall not be used.

Indicate clearly conditions that are:

- absolutely contraindicated,

- contraindicated but may be used under special circumstances and what precautions should be taken in such cases.
- If no information is available for this section, state "Unknown".

5.16 Warnings and Precautions

Briefly state warnings and precautions necessary to ensure safe use of the product, e.g. caution against giving to children and elderly; use in pregnancy and lactation; in infants; etc.

If no information is available for this section, state "Unknown".

5.17 Drug Interactions

State only interactions that are observed and/or for which there is potential clinical significance. Interactions may occur with

- other medicinal products used;
- other herbs/ substance;
- meals, or specific types of food.

If no information is available for this section, state "Unknown".

5.18 Pregnancy and Lactation

State any effect on pregnancy and lactation, if applicable.

5.19 Side Effects/ Adverse Reactions

State in order of severity and frequency, the side effects, adverse reactions, toxic effects, etc. (i.e. reactions, toxic effects, other than those desired therapeutically). This included reactions such as allergy, hypersensitivity, dependence, addiction, carcinogenicity, tolerance, liver/ kidney toxicity, etc.

Indicate symptoms and sites of effects/reactions.

- Reactions, whether minor or serious, shall be stated.
- Severity, reversible, frequency of occurrence shall be indicated wherever possible.
- Clinical tests for detection of 'sensitive' patients, measure for management of adverse reactions developed shall be described wherever possible.

If no information is available for this section, state "Unknown".

5.20 Signs and Symptoms of Overdose and Treatment

Briefly state symptoms of overdose/ poisoning, and where possible, recommended treatment and antidotes for overdose/ poisoning.

If no information is available for this section, state "Unknown".

5.21 Storage Conditions

State the recommended storage conditions (specific temperature, eg: 30°C, humidity, light, etc.).

Information shall include storage condition before first opening, after reconstitution and/or after opening and for all the listed pack types where applicable. Stability data to support such storage condition shall be made available.

5.22 Shelf Life

The shelf life for all the listed pack types shall be supported by stability data.

Information shall also include shelf life before first opening, after reconstitution and/or after opening where applicable. Stability data to support such shelf life shall be made available.

Evidence is required to demonstrate that the product is stable (meets the finished product shelf life specifications throughout its proposed shelf-life).

5.23 Therapeutic Code (if any)

Select "Health Supplement".

SECTION B: PRODUCT FORMULA

Change of formulation for active ingredient or excipient is not allowed during product evaluation.

5.24 Batch Manufacturing Formula (BMF)

State the batch size and actual batch manufacturing master formula. Data from validation step will be captured in terms of substance name, type (active ingredient or excipient), function and quantity per unit dose. Other information will need to be entered.

An **attachment** of the Batch Manufacturing Formula documentation must be provided. The documents must be verified by authorized personel.

Example of BMF documentation:

ABC Sdn. Bhd.
Batch Manufacturing Formula
Product Name:
Batch Quantity: 1,000,000 capsules

Name	Function	Quantity per capsule	Batch quantity	Overage
Pyridoxine HCl	Active	_ mg	_ kg	_ %
Cholecalciferol	Active	_ mg	_ kg	_ %
Glycerin	Excipient	_ mg	_ kg	None
Gelatin	Excipient	_ mg	_ kg	None
Purified water	Excipient	0 mg *	_ kg	None
		Total: _ mg	Total: _ kg	

* evaporated, does not exist in final formulation

(Signature)
Post of authorized person
Name of authorized person
Date:

SECTION C: PARTICULARS OF PACKING

5.25 Packaging

- Maximum pack size allowed for tablets, pills, or capsules is based on daily dosing for a quantity not exceeding six (6) months usage.

- Maximum pack size allowed for products with disease risk reduction claim is for one (1) month supply of products unless justified.

- Product with dosage form of soft gel with tail (twist and squeeze) shall come with children proof cap.

- Packaging particulars to the listing of packing as follows ;

- C1: pack size and fill details by weight, or volume or quantity;
- C2 : container type
- C3 : Barcode/ serial No (optional);
- C4 : recommended distributor's price (optional);
- C5 : recommended retail price (optional);

SECTION D: LABELLING REQUIREMENTS

5.26 Product label

The following information shall be present on the label of a product at the outer carton, immediate container or blister/ strips:

Refer to specific Appendix for:

a) **Appendix 19 : General Labelling Requirements**
Label (mock-up) for immediate container and outer carton;

b) **Consumer Medication Information Leaflet (RiMUP)**
For health supplement with high claims/ disease risk reduction

c) **Appendix 20 : Specific Labelling Requirements**
For specific substances, e.g. alfalfa, arginine, bee pollen, chitosan, Boswellia serrata etc.

Additional Requirements for Labelling:

- Information on the Product Name, and Name and Strength of active ingredient(s) must be printed repeatedly (for blister/ strip).
- Product with dosage form of soft gel with tail (twist and squeeze) shall include the statement 'Under parent supervision' in the label.
- For products containing animal origin(s), add this statement: *This product contains substance(s) from animal origin.*
- For products containing porcine, add this statement: *This product contains animal part(s) (porcine/pig).*

Health supplement products with disease risk reduction claims (high) are encouraged to be dispensed under the supervision of pharmacists or medical practitioners. At such, the label and package insert of health supplement products with disease risk reduction claims (high) shall have the following statement**:**

"Please consult a doctor/ pharmacist before taking this product".

5.27 Standard Labelling for Health Supplements

- Name and Strength of active substances
- RDA (optional)
- Preservative(s) (where present)
- Alcohol (where present)

- Indication
- Dose / Usage Instruction

- Functional Claim (if applicable)
- Warnings (If applicable)

- Storage Condition
- Keep out of reach of children / Jauhkan daripada capaian kanak-kanak

PRODUCT NAME

GRAPHIC

- Pack Size
- Dosage Form

- Name & address of Product Registration Holder
- Name & address of Manufacturer

- Sources (animal origin)
- Source of capsule shell (if applicable)

- Batch Number
- Manufacturing Date
- Expiry Date

MAL ……..

Note:

- *Product label shall follow the standard labelling for Health Supplement.*
- *Information stated on the left and right panel is interchangeable.*
- *All information on the label must be truthful and not misleading to the consumers.*
- *Batch number, manufacturing date, expiration date can be stated on the label, on top of the cap or bottom of the bottle.*
- *The front panel must contain the information as above. However, the information on the side panels is interchangeable. Additional cautionary labelling relating to the safety of the product may be imposed.*

5.28 Prohibited Visual/ Graphics on Label, as shown in **Table 7** below:

- The label should not contain any statement or visual presentation which, whether directly or by implication, is likely to mislead the consumer about any product.
- The graphics printed on the outer and inner labels have to be standardized to avoid confusion to the customers.

No.	Issue	Example	Note
1.	Marketing strategy	**Example:** "Money back guarantee" "Buy 1 free 1" "Backed by RM5 million product Liability Insurance"	Such statements are prohibited on labels.
2.	Usage guide which promotes use of other product(s)	**Example:** "After consumption of this product (Product A), for better results, it is recommended to take Product B"	Prohibited on product label
3.	Consumer testimonial		Prohibited on product label
4.	Clinical Trial results or any information on clinical trial done on product	Example: "Clinically Tested" "Randomized Double-Blind Placebo Control Clinical Study"	Such statements are prohibited on labels.
5.	Reference to Hadith/ Al-Quran/ Bible/ Religious books		Prohibited on product label
6.	Opinion of prominent figure(s) on product or its active ingredient/ content	**Example:** Opinion of product/ formulation inventor	Prohibited on product label

No.	Issue	Example	Note
7.	Label design (graphic and color) similar to labels from another company		Prohibited on product label
8.	Statement on active ingredient origin	**Example:** Source from the Mountains of Alps	Allowed if proven true
9.	Introduction of founder/ Manufacturer		Prohibited on product label
10.	Logo with certification	**Example:** SIRIM/ ISO / GMP/ HACCP	Prohibited on product label because certification renewal is on a yearly basis
11.	Name/ Statement/ Logo/ registered trademark which does not satisfy the specifications	**Example:** "Dr. ABC's Formula" "Nothing like it"	Prohibited on product label
12.	Special technique used/ superiority in ingredients	**Example:** Capsule coat	Allowed if proven true
13.	Nutritional claims with analysis certificate attached	**Example:** Calorie, Fat, Protein and others	Prohibited on product label
14.	Graphics or picture of internal organs	**Example:** Kidney, Heart, Nerves.	Prohibited on product label
15.	Gender symbol (male or female)	(♀ and/or ♂)	Prohibited on product label
16.	Indecent photographs/ pornography/ graphics/ images		Prohibited on product label

No.	Issue	Example	Note
17.	Graphics which are incoherent with the indication	**Example:** - Noted indication is for constipation, but graphics on label shows a slim-looking lady which denotes indication for weight loss - Indication for urination but label graphics contains picture of a water hose.	Prohibited on product label
18.	Highlighting unnecessary body parts	**Example:** Indication is for general health but graphics on label highlights male and female sexual organ parts	Prohibited on product label
19.	Graphics of plants or animal which may cause confusion	**Example:** Radix Ginseng which is improvised as a male sexual part	Prohibited on product label
20.	Photograph of celebrities	**Example** - Artiste, sports person(s), politician	Prohibited on product label
21.	Statement on sugars	**Example** - This product contains no added sugar	Allowed on product label provided the product contains no fructose, glucose, sucrose, or other kind of sugars with a potential to affect diabetics are not included in the formulation
22.	Negative statement	**Example** - No gluten, yeast etc	Prohibited on product label
23.	Other statements	**Example:** - This product is blended with premium quality - Certified chemical residue free	Prohibited on product label

No.	Issue	Example	Note
24.	Label design (graphic/ colour) similar to/ same as an adulterated product		Prohibited on product label

Notes:

1. *The list is not meant to be exhaustive and will be reviewed from time to time.*
2. *The Authority reserves the right to disallow any other words, phrases or graphics for product label, which in its opinion is misleading, improper or not factual.*

5.29 Package insert (Optional)

The following information is required to be included in a package insert:

(i) Brand or Product Name
(ii) Name and Strength of Active Substance(s)
(iii) Product Description
(iv) Indication
(v) Dose/ Use Instruction
(vi) Contraindications
(vii) Warnings and Precautions
(viii) Interactions with Other Medications
(ix) Statement on usage during pregnancy and lactation
(x) Adverse Effects/ Undesirable Effects
(xi) Overdose and Treatment
(xii) Storage Conditions (may be omitted if the information is stated on the label or outer carton labels)
(xiii) Dosage Forms and packaging available
(xiv) Name and Address of manufacturer/ product registration holder
(xv) Date of Revision of Package Insert

SECTION E : PARTICULARS OF PRODUCT OWNER, MANUFACTURER, IMPORTER AND OTHER MANUFACTURER(S) INVOLVED AND STORE ADDRESS

5.30 Product Owner

Please select whether the product owner is the product holder, manufacturer or both.

If the product owner is neither the product holder nor the manufacturer, please select name and address of the product owner (applicable for imported product only).

Other details such as product owner, manufacturer, repacker, other manufacturer involved in the manufacturing process, store address and importer (if any) are required to be filled. It is mandatory for the repacker to acquire GMP certificate.

5.31 Letter of authorization from product owner

This is applicable for imported product in which the product owner appoints the product holder (in Malaysia) as their product holder in Malaysia

5.32 Letter of appointment of contract manufacturer and/ or repacker

This applies if the product is contract manufactured by a manufacturer who is not the product owner.

5.33 Letter of acceptance from contract manufacturer and/ or repacker

This applies if the product is contract manufactured by a manufacturer who is not the product owner.

5.34 Certificate of Pharmaceutical Product (CPP), Certificate of Free Sales (CFS) and Good Manufacturing Practice (GMP)

CPP can be submitted in replacement of CFS and GMP certificate if the product is classified as a pharmaceutical product in the country of origin:

5.35 GMP/ CFS Template

Authority name, address, country

Type of certificate

Company name (product owner/ manufacturer)
Product name
Product formulation if available
Dosage form

Statement of freely sold (similar meaning) if for CFS certificate
Standard of GMP and compliance status if for GMP certificate
Duration of certification

Name, signature and designation of authorized personnel
Date of signature

Note: The certificate must be in English or translated into English (certified true by issuance or embassy or notary public)

5.36 Attachment of Protocol Analysis

Protocol analysis is attached here. (Part of quality of product-Section P: Drug Product)

SECTION P: DRUG PRODUCT

5.37 Manufacturing Process

Provide a brief description of the manufacturing process. Provide essential points of each stage of the manufacturing process and a description of the assembling of the product into final containers. If the product is repacked/assembled by another manufacturer, provide details of repacking/assembly and quality control.

The manufacturing process may be presented in the form of a flowchart.

5.38 Control of Critical Steps and Intermediate/In Process Quality Control (IPQC)

Provide a summary of the tests performed, stages at which they are done, and the frequency of sampling and number of samples taken each time. Provide specifications for quality assurance of the product. **Example of In Process Quality Control:**

Company Name/ Address:

Applicant/ Client Name/ Address:

Date:

In-Process Quality Control: Test performed during manufacturing process

No.	Test Done (example)	Stage Done (example)	Frequency of testing (example)	Quantity sample taken (example)	Specifications (example)	Method (example)
1.	Appearance	Before weight, after encapsulation	2	10 gram	Blue like orange	Organoleptic test
2.	Disintegration	After compression	2	10 tablet	NMT 30 minutes	Equipment etc.
3.	Uniformity of weight	After tableting, Packaging	4	20 Tablets	1 gram/tab	

* Declaration (if any)
Signature (authorized personnel)
Name:
Designation:

*** The above parameters are only as an example; other test may be required for specific**

5.39 Finished Product Quality Control

a) Provide details of quality control specifications, including a list of tests for both release and shelf life specifications (if they are different) and state the limits of acceptance.

Example of Finished Product Quality Specification :

Finished Product Quality Control (FPQC) - Finished product Specification/ Specification Sheet

Company name/Address:
Product Name:
Batch no.
Dosage form:
Packaging:
Date of manufacture:
Date of expiry:

No.	Test	Method	Specification	Reference
1.	Appearance/ Organoleptic: Odour Colour	Ex: Macroscopic/ Microscopic	To describe the characteristic	In-house/ pharmacopoeia (e.g. BP/USP etc.)
2.	Assay: (All active ingredients/ compounds claim on label)	HPLC/ GC/ MS/ UV	To specify	To specify
3.	Disintegration/Dissolution	To specify	DRGD	DRGD
4.	Uniformity of weight	To specify		
5.	Water content	To specify		
6.	Microbial contamination TAMC, TYMC, specified microorganism	To specify	DRGD	DRGD
7.	Heavy Metal Contamination: Lead, Arsenic, Cadmium, Mercury	To specify	DRGD	DRGD
8.	Etc.:			

Signature:
Name:
Designation: (At least by Quality Assurance Manager or equivalent)
Date of signature:

*** The above parameters are only as an example; other test may be required for specific product.**

b) **Certificate of Analysis of Finished Product**

- The Certificate of Analysis of Finished Product must be complete with the product specification and result. The list of tests and specifications must be same with finished product specification document.

- Effective from 1 January 2018, **two (2) batches of Certificate of Analysis (CoA) of Finished Product** must be submitted for new product registration of Health Supplement products with general claim.

  (Reference: Directive No. 3, 2017, *BPFK/PPP/07/25(8)Jld.1*: *Direktif Untuk Menguatkuasakan Keperluan Sijil Analisa Produk Siap* (Certificate of Analysis (CoA) For Finished Product*) Semasa Permohonan Pendaftaran Baru Produk Semulajadi dan Produk Suplemen Kesihatan Dengan* General Claims) (15 February 2017)

Example of Certificate of Analysis for Finished Product (Health Supplement)

Certificate of Analysis

Company name/ Address :

Product Name :

Batch no. :

Dosage form :

Packaging :

Date of manufacture :

Date of expiry :

Test Parameter	Specifications	Results	Method
Appearance/ Organoleptic: Odour Colour	To describe the characteristic		
Disintegration	DRGD		
Uniformity of weight			
Assay: (All active ingredients/ compounds claim on label)	To specify		
Microbial Contamination Test TAMC, TYMC, specified microorganism	DRGD		
Heavy Metal Contamination			
Lead (Pb)	NMT 10 ppm		
Cadmium (Cd)	NMT 0.3 ppm		
Mercury (Hg)	NMT 0.5 ppm		
Arsenic (As)	NMT 5 ppm		

NMT = Not More Than

Signature :
Name :
Designation : (At least by Quality Control Manager or equivalent)
Date of signature :

Note: The above parameter are only as an example, other tests may be required for specific product.

c) **Quality Control Test for Health Supplement Product** are:

1. Limit Test for Heavy Metals

a) Lead : NMT 10.0 mg/kg or 10.0 mg/litre (10.0ppm)
b) Arsenic : NMT 5.0 mg/kg or 5.0 mg/litre (5.0ppm)
c) Mercury : NMT 0.5 mg/kg or 0.5 mg/litre (0.5ppm)
d) Cadmium : NMT 0.3 mg/kg or 0.3 mg/litre (0.3ppm)

** Required for products with ingredients from natural sources.*
The test shall be conducted on the finished product.

2. Disintegration Test (for tablets, capsules and pills)

Disintegration time:

a) Uncoated tablets : NMT 30 minutes
b) Film-coated tablets : NMT 30 minutes
c) Sugar-coated tablets : NMT 60 minutes
d) Enteric-coated tablets/capsules :
Does not disintegrate for 60 minutes in acid solution but to disintegrate within 60 minutes in buffer solution; OR
Does not disintegrate for 120 minutes in acid solution but to disintegrate within 60 minutes in buffer solution

e) Capsules : NMT 30 minutes
f) Pills : NMT 120 minutes

3. Test for Uniformity of Weight (tablets and capsules only)

a) Tablet

- For tablet with average weight of 130mg or less: Not more than 2 tablets differ from the average weight by more than 10% AND no tablets differ from the average weight by more than 20%
- For tablet with average weight between 130-324mg: Not more than 2 tablets differ from the average weight by more than 7.5% AND no tablet differs from the average weights by more than 15%
- For tablets with average weight more than 324mg: Not more than 2 tablets differ from the average weight by more than 5% AND no tablet differs from the average weight by more than 10%

b) Capsule

Individual weight of the capsule to be within the limit of 90-110% of the average weight.

4. Tests for Microbial Contamination, as shown in **Table 8** below:

Route of Administration	TAMC (CFU/g or CFU/ml)	TYMC (CFU/g or CFU/ml)	Specified microorganisms
Non-aqueous preparations for oral use	NMT 2 x 10^3	NMT 2 x 10^2	Absence of *Escherichia coli* (1 g or 1 ml)
Aqueous preparations for oral use	NMT 2 x 10^2	NMT 2 x 10^1	Absence of *Escherichia coli* (1 g or 1 ml)
Special Ph. Eur. provision for oral dosage forms containing raw materials of natural (animal, vegetal or mineral) origin for which antimicrobial pretreatment is not feasible and for which the competent authority accepts TAMC of the raw material exceeding 10^3 CFU/g or CFU/mL.	NMT 2 x 10^4	NMT 2 x 10^2	Not more than 10^2 CFU of bile-tolerant gram-negative bacteria (1 g or 1 ml or MPN) Absence of *Salmonella* (10 g or 10 ml) Absence of *Escherichia coli* (1 g or 1 ml) Absence of *Staphylococcus aureus* (1 g or 1 ml)

Notes:

TAMC : Total Aerobic Microbial Count [Not applicable to products containing viable microorganisms as active ingredient (Example: product containing probiotics from bacteria)]

TYMC : Total Yeasts & Moulds Count [(Not applicable to products containing viable microorganisms as active ingredient (Example: product containing probiotics from yeasts)]

NMT : Not more than

[Reference: latest version of British Pharmacopoeia]

d) **Other supporting documents**

- For the submission of other supporting documents.
- Additional requirement for safety and quality of active ingredient/ product (e.g., dose for children, pregnant etc.)
- Quality testing for specific ingredient:
  - For product containing Aphanizomenon flos-aquae, applicants would have to provide certificates of analysis showing that the microcystin-LR or total microcystins content of the raw material does not exceed 1µg/g and the finished product has been tested for microcystin-LR using an acceptable method.
  - For products containing probiotics, applicants are required to provide strain specific antibiotic resistance data for each probiotic strain.

- For products containing Red Yeast Rice (Monascus purpureus), applicants shall provide certificates of analysis (for both raw material and finished product) showing the Monacolin-K content. The percentage of Monacolin-K shall not exceed 1% and the Monakolin-K consumed shall not exceed 10 mg per day.

➢ Quality testing for specific product:
- Certificate of Analysis for the level of dioxin (PCDDs and PCDFs) and dioxin-like polychlorinated biphenyls (PCBs) is required for product containing ingredient(s) derived from seafood. *(The acceptable limit for these tests shall follow standard references such as United States Pharmacopoeia (USP) and European Regulation.)*
- Certificate of Analysis for proof of hormone-free is required for product containing placenta

5.40 Stability Data

General:

- The stability of the product is important to ensure the quality of health supplement product. This is to ensure that the product specifications are maintained throughout the shelf life of product.

- Effective from 27 November 2014, a shelf life of two (2) years shall be approved for both local and imported products. Proposed shelf life exceeding this period will have to be supported by stability study data conducted in Malaysia under Zone IVb conditions (30±2 °C, 75±5%). For further information, refer to circular: Bil.(27).dlm BPFK/PPP/06/04_Jld.7 *Tempoh Hayat Simpanan* (Shelf-Life) *Bagi Produk Tradisional dan Suplemen Kesihatan* (27 November 2014).

- The testing frequency of the stability data is as described in **Table 9** below:

Storage condition	Testing frequency
Real time	Time 0, 3, 6, 9, 12, 18, 24 months and annually there after through
Accelerated	0, 3 and 6 months

Refer to the ASEAN Guidelines on Stability Study and Shelf Life of Health Supplements for further details.

Storage Conditions with Type of Container Closure System/ Stability Study

Table 10:

No.	Type of Container Closure System/ Study	Storage Condition
1.	Products in primary containers permeable to water vapour	30°C ± 2°C/75% RH ± 5%RH
2.	Products in primary containers impermeable to water vapour	30°C ± 2°C
3.	Accelerated studies	40°C ± 2°C/75% RH ± 5%RH

Reports of stability studies shall provide details of:

- the batches placed under study (a minimum of 2 batches are required).
- containers/ packaging type.
- conditions of storage during study (temperature, humidity, etc).
- duration of study and frequency (interval) of the tests/ observations.
- the tests performed and acceptance limits.

Example of Stability Data

STABLITY DATA

PRODUCT NAME : TABLET ABC 500MG **BATCH NO.** :

MANUFACTURING DATE: dd/mm/yy **TEMPERATURE:** 30 °C ± 2 °C

EXPIRY DATE : dd/mm/yy **RELATIVE HUMIDITY** : 75 % ± 5%

Tests	Specification	Frequency of Testing							
		0	3	6	9	12	18	24	36
Product description	Film-coated tablet, brownish in colour								
Disintegration test	NMT 30 minutes								
Assays	eg: 90% -120% (ref....)								
Microbial Contamination test: Total Aerobic Microbial Count Total Yeasts & Moulds Count Test for Specified Microorganisms	 NMT 2 x 10^4 NMT 2 x 10^2 ➢ NMT 1 x 10^2 CFU of bile-tolerant gram-negative bacteria in 1g or 1ml or MPN ➢ Absence of Salmonella in 10g or 10ml ➢ Absence of Escherichia coli in 1g or 1ml ➢ Absence of Staphylococcus in 1g or 1 ml								
Heavy metal test: Lead Arsenic Mercury Cadmium	 ≤10.0 mg/kg (≤ 10ppm) ≤5.0 mg/kg (≤ 5ppm) ≤0.5 mg/kg (≤ 0.5ppm) ≤0.3 mg/kg (≤ 0.3ppm)		NA						

Conclusion ----------

Analyst name: (signature)
Name:
Designation
Date:

Verified by: (signature)
Name:
Designation
Date:

Stability study data checklists are as in **Table 11** below:

Data Required	Remarks
Company name	- From product holder/ manufacturer/ third party lab
Product name	- To be same with other documentation
Dosage form	- To be same with A3
Packaging particulars	- Material and pack size must be stated - To be same with C1
Storage condition	- Temperature and humidity must be stated - Shall comply with ASEAN Zone IV requirement (30±2°C/75±5%RH) - If different storage condition (e.g. 25°C, 2-8°C), must provide justification/ supporting data.
Frequency of testing	For example: - 0, 3, 6, 9, 12, 18, 24 months and annually for the proposed shelf life
List of relevant tests	- All tests required for each dosage form shall be conducted, for example: o Physical appearance changes o Disintegration test (if applicable) o Chemical Assays for active ingredients (if applicable) o Microbial tests
Specifications	- Acceptance limit for each test must be stated - To be supported by established references (e.g. USP, BP) if available
Results for each test	- Must meet the specifications
Approval by authorized person	- Must have the name, post and signature of authorized person

Testing Parameters of Stability Study for each type of dosage forms are shown in **Table 12** below:

Testing Parameters / Dosage Form	Appearance/ organoleptic (odor, color, taste)	Assay*	Hardness/ friability	Disintegration or dissolution rate	Moisture content	Viscosity	pH	Microbial content	Granules/ Particle Size variation	Re-suspendability
Oral powder	√	√			√			√		
Hard capsule	√	√		√	√			√		
Soft capsule	√	√		√				√		
Coated and Uncoated Tablet	√	√	√ (uncoated)	√	√			√		
Coated and Uncoated Pill/ Pellet	√	√		√	√			√		
Suspension	√	√				√	√	√	√	√
Solution	√	√				√	√	√		
Emulsion	√	√				√	√	√		
Granules	√	√			√			√	√	

Notes:

1. The list of tests for each product is not intended to be exhaustive, nor is it expected that every listed test to be included in the design of the stability study protocol for a particular finished product.

** Assay to determine the stability of a single active ingredient or a single marker/surrogate indicator that is susceptible to change during storage and is likely to influence quality shall be sufficient to infer the overall stability of the TM/HS product irrespective of whether the finished product contains single or multiple active ingredients.*

2. Justification must be given if one of the tests is not conducted for relevant dosage form.

SECTION S: DRUG SUBSTANCE

5.41 Specifications and Certificate of Analysis of Active Ingredient

Certificate of analysis for each active ingredient (raw material) is required pre-registration. The certificate must consist of specifications and results of analyses.

ATTACHMENT 1

CHECKLIST OF DOSSIER REQUIREMENT FOR HEALTH SUPPLEMENTS

- Depending on the level of claims, submission may follow the route outlined:
  i) General/ Nutritional and Medium Claims - Abridged evaluation
  ii) Disease Risk Reduction Claims - Full evaluation

Table 13: Checklist for General/ Nutritional and Medium Claim

No.	Field	General or Nutritional Claims	Functional Claims
Product Validation (PV)			
PV1	Brand Name	√	√
	Full Product Name		
PV2	Dosage Form	√	√
	- COA capsule shell is required		
	- Colouring agent used in capsule		
	- Letter to verify the source of gelatin used		
PV3	List of Active ingredient(s)	√	√
PV4	List of excipient (s)	√	√
PV5-17	Other information (e.g., Manufacturer,premix etc., where applicable)	√	√
Part 1			
A4	Product Description	√	√
	- Describe visual and physical characteristics of the product including shape, size, superficial markings, colour, odour, taste, type of coating, type of capsule etc. where applicable		
	- Animal shape is only allowed for 'For Export Only' (FEO) Products		
A7	Product indication/ Usage	√	√
A8	Dose/ Use Instruction	√	√
	- Target population (e.g., Adults)		
	- Quantity and frequency		
	- Dosing schedule must be stated (e.g. take before/ after/ with meal)		
A10	Contraindication, if applicable	√	√
A11	Warning/ Precautions, if applicable	√	√

No.	Field	General or Nutritional Claims	Functional Claims
A12	Drug Interaction, if applicable	√	√
A14	Side Effects/ Adverse Reactions, if applicable	√	√
A15	Signs and Symptoms of overdose and treatment, if applicable	√	√
A19	Storage Condition - According to stability data	√	√
A20	Shelf life - Must be supported by stability study - Please refer subsection 5.40	√	√
B1.1	Batch Size	√	√
B1.2	Batch Formula	√	√
B2	Attachment of Batch Manufacturing Formula - Shall be on the product owner's/ manufacturer's original letterhead, product details, date and signature & designation of authorized personnel	√	√
C	Pack Sizes	√	√
	- Material and colour used for primary and secondary packing should be stated	√	√
D1	Label for immediate container	√	√
D2	Label for outer carton (if applicable)	√	√
D3	Proposed package insert / Product information leaflet (if applicable)	√	√
E1	Company name and address of product owner	√	√
	Letter of authorization from product owner to product registration holder (if applicable)	√	√
E2	Letter of Appointment of Contract Manufacturer/ Repacker from Product Owner (if applicable)	√	√
	Letter of Acceptance from Contract Manufacturer/ Repacker (if applicable)	√	√
E3	Certificate of Pharmaceutical Product (CPP) - Applicable to imported products, must be issued by the competent authority in the country of origin. CPP issued by reference country may be considered.	√	√

No.	Field	General or Nutritional Claims	Functional Claims
E4	Certificate of Free Sale (CFS) - Applicable if CPP is not available, must be issued by the competent authority in the country of origin/ products owner country.	√	√
E5	Certificate of Good Manufacturing Practice (GMP) - Applicable if CPP is not available, must be issued by the competent authority in the manufacturing country.	√	√
E6	Company name and address of manufacturer	√	√
E7	Company name and address of other manufacturer (if applicable)	√	√
E8	Importer(s)	√	√
E9	Store address(s)	√	√
E12	Attachment of protocol analysis	√ - dosage form extended/ sustained-release/ timed-release dosage form * LOC to submit during post registration for other types of dosage form	√
E14	Examples of supporting documents		
	Dioxin level test results (for product containing ingredients derived from seafood)	√	√
	Certificate of Good Manufacturing Practice (GMP) for premixed active ingredients		
	Hormone free test results (for placenta products)		

No.	Field	General or Nutritional Claims	Functional Claims
	Declaration letter from product manufacturer on the hormone - free status for product containing placenta		
	Manufacturing process validation report if applicable		
	Letter of commitment if applicable		
	Etc.		
Part II Section P			
P3.2	Manufacturing Process	√	√
P3.2.1	Attachment of Manufacturing Process Document or Manufacturing Flow Diagram	√	√
P3.3	In-Process Quality Control (IPQC)	√ *LOC to submit data during post registration	√
P5.1	Finished Product Specification (FPQC)	√ * LOC to submit data during post registration	√
P5.4.1	Attachment of Certificate of finished product (COA of finished product)	√	√
P8	Stability Data	√ ***Please refer subsection 5.40)	√
Part II Section S			
S4.1 & S4.4.1	Attachment of Specifications and Certificate of Analysis (COA) of Active Ingredient	√	√
* Complete stability study conducted at 30 ± 2 ºC / RH 75 ± 5%, IPQC, FPQC, protocol analysis and COA of finished product are required to be submitted 2 years after product registration with SAMPLE of the products. Failure on submission will cause the product be suspended until the complete documents are submitted, the registration of the product will be terminated if the complete documents still cannot be produced upon renewal of product registration.			

- Dossier Requirement for Disease Risk Reduction as in **Table 13** above and **Table 14** below:

Table 14: Additional Quality Data Checklist for Disease Risk Reduction Claim

No.	Field	Disease Risk Reduction Claim
PART P	**P. HEALTH SUPPLEMENT PRODUCT** P1. Description and Composition P2. Pharmaceutical Development P2.1 Information on Development Studies P2.2 Components of the Health Supplement Product P2.3 Finished Product P2.4 Manufacturing Process Development P2.5 Container Closure System P2.6 Microbiological Attributes P2.7 Compatibility P3. Manufacturer P3.1 Batch Manufacturing Formula P3.2 Manufacturing Process & Process Control P3.2.1 Manufacturing Process Flowchart P3.3 Control of Critical Steps & Intermediates P3.4 Process Validation and Evaluation P4. Control of Excipients P4.1 Specifications P4.2 Analytical Procedure P4.3 Validation of Analytical Procedures P4.4 Justification of Specification P4.5 Excipient of Human or Animal Origin P4.6 Novel Excipients P5. Control of Finished Product P5.1 Specification P5.2 Analytical Procedures P5.3 Validation of Analytical Procedures P5.4 Batch Analyses P5.5 Characterization of impurities P5.6 Justification of Specification P6. Reference Standards or Materials	√

No.	Field	Disease Risk Reduction Claim
	P7. Container Closure System P8. Stability P9. Product Interchangeability/Equivalent evidence	
PART S	**S. HEALTH SUPPLEMENT SUBSTANCE** S1. General Information S1.1 Nomenclature S1.2 Structure S1.3 General Properties S2. Manufacture S3. Characterisation S4. Control of Health Supplement Substance S4.1 Specification S4.2 Analytical Procedures S4.3 Validation of Analytical Procedure S4.4 Batch Analysis S4.5 Justification of Specification S5. Reference Standards or Materials S6. Container Closure System S7. Stability	√

PART III: NON-CLINICAL DATA

- Applicable to disease risk reduction claims
  (For new active ingredient, new combination of active ingredients and new dose)

Table 15:

No.	Field	Disease Risk Reduction Claims
1.	Overview of non-clinical testing strategy	√
	- nomenclature	
	- structure	
	- general properties	
2.	Pharmacology	√
	- related information (including academic literature) of pharmacology studies on the declared efficacy	
3.	Pharmacokinetics	√
	- related information (including academic literature) of pharmacokinetics studies on the declared efficacy	
4.	Toxicology	√
	- related information (including academic literature) of toxicology studies	
5.	Integrated overview and conclusions	√
6.	Other toxicity studies if available	√
7.	References	√
	- List of references used	

- All information must be provided in the following format/ table:

Study Title	Type of Study	Product (formulation)	Study Summary	Summary findings
			- Study Design (e.g. case control, randomised placebo controlled, in vitro data, cohort study) - Dosage - Subject - Study Duration - Outcome parameters	(Includes scientific details such as strength of evidence [e.g. p-values], conclusions, any shortcomings, etc. For traditional evidence include enough information to demonstrate relevance)

PART IV: CLINICAL DOCUMENTS

- Applicable to disease risk reduction claims (for new active ingredient, new combination of active ingredients and new dose).

Table 16:

No.	Field	Disease Risk Reduction Claims
1.	Clinical overview	√
2.	Production Development Rational	√
3.	Overview of Biopharmaceutics	√
	- To include associated analytical methods	
4.	Overview of Clinical Pharmacology	√
	- Summary of clinical pharmacology studies	
5.	Overview of Efficiency	√
	- Summary of clinical efficacy	
6.	Overview of Safety	√
	- Summary of clinical safety	
7.	References	√
	- List of all clinical studies	
	- List of key literature references	
	- Published clinical papers	

- All information must be provided in the following format/table:

Forms of study	Sample size	Duration	Randomisation of groups	Endpoint	Statistical analysis of data
Randomised, controlled, and preferably blinded intervention studies	Must be justified and must involve sufficiently large number of subjects to estimate incidence and nature of potential adverse reactions	Must be justified and must be of sufficient duration to ensure no safety concerns with respect to long term use	All groups shall have comparable baseline values, particularly for those factors that are known to be, or may be, confounders or risk factors	As a decrease incidence of the disease or a reduction of a factor, or a surrogate thereof, of the many that contribute to the development of a disease	Methods to calculate the sample size, setting the power and the significance level at conventional 80% and $p<0.05$ respectively shall be utilised Meta-analysis shall combine only studies with similar design, populations, interventions and outcome measure

ATTACHMENT 2

Table 17: Allowable claims for specific active ingredients in HS products

Ingredients	Claims		
	General	**Functional**	**Reduced Risk Reduction Claim**
Alpha$_{s1}$-Casein Tryptic Hydrolysate (Milk Protein Hydrolysate)	• Helps in maintenance of good health	• Promotes/ Improves sleep quality • Promotes relaxation	
Beta Carotene	• Maintenance of good health	• Helps in maintenance of growth, vision and tissue differentiation	
Biotin	• Helps in maintenance of good health	• Helps to metabolize fats and carbohydrates	
Calcium	• Helps in maintenance of good health	• Helps in the formation and maintenance of bones and teeth • Claim for specific subgroup: - Additional calcium is required for pregnant and lactating women, when diet does not provide a sufficient daily intake to help in proper bone formation in developing baby	

Ingredients	Claims		
	General	Functional	Reduced Risk Reduction Claim
Chondroitin Sulphate	• Helps in maintenance of good health	• Promotes healthy joint	
Citicoline	• Helps in maintenance of good health	• Helps to support healthy cognition	
Coenzyme Q10	• Helps in maintenance of good health	• Supports heart health	
Collagen Hydrolysate	• Helps in maintenance of good health	• Promotes healthy joints	
Copper	• A factor in maintenance of good health	• Helps in the formation of red blood cell	
Docosahexaenoic acid (DHA)	• Helps in maintenance of good health	• Supports heart health • Supports brain health • Helps to maintain healthy level of triglycerides • Supports eye health • For fetal brain and eye development	
Eicosapentaenoic acid (EPA)	• Helps in maintenance of good health	• Supports heart health • Supports brain health • Helps to maintain healthy level of triglycerides	
Fish Oil	• Helps in maintenance of good health	• Supports joint health	

Ingredients	Claims		
	General	**Functional**	**Reduced Risk Reduction Claim**
Folic Acid	• Helps in maintenance of good health	• Helps in formation of red blood cell • For fetal development	• Helps prevent neural tube defects for women who are planning a pregnancy before conception and during 12 weeks of pregnancy at a dose of 400 mcg daily
Fructooligosaccharides	• Helps in maintenance of good health	• Promotes the growth of good bacteria living inside the gut	
Hovenia dulcis Fruit	• Helps in maintenance of good health	• For maintenance of good liver health	
Hyaluronic Acid	• Helps in maintenance of good health	• Maintains healthy skin	
Iodine	• Helps in maintenance of good health	• Helps in the function of the thyroid glands	
Iron	• Helps in maintenance of good health	• Helps in the formation of red blood cell	• Helps to prevent iron anemia • Helps to prevent anemia due to iron deficiency
L-Carnitine	• Helps in maintenance of good health	• Helps to aid fat metabolism	

Ingredients	Claims		
	General	**Functional**	**Reduced Risk Reduction Claim**
Lutein	• Helps in maintenance of good health	• Supports eye health	
Magnesium	• Helps in maintenance of good health	• Helps the body to metabolize carbohydrate	
Manganese	• A factor in maintenance of good health	• Helps to metabolize carbohydrates and proteins	
Mixed Tocotrienols	• Helps in maintenance of good health	• Supports brain health	
Monascus purpureus (Red yeast rice)	• Helps in maintenance of good health	• Helps maintain healthy cholesterol levels	
Phosphorus	• Helps in maintenance of good health	• Helps in the formation and maintenance of bones and teeth	
Probiotics	• Helps in maintenance of good health	• Helps to improve a beneficial intestinal microflora • Helps support gastrointestinal health	
Vaccinium macrocarpon (Cranberry) Fruit	• Helps in maintenance of good health	• Supports healthy urinary tract	

Ingredients	Claims		
	General	Functional	Reduced Risk Reduction Claim
Vitamin A	• Maintenance of good health	• Helps to maintain growth, vision and tissue development • Aids in maintaining the health of the skin and mucous membrane • Aids in maintenance of eye health	
Vitamin B1 (Thiamine)	• Helps to maintain good health	• Helps in maintenance of growth, vision and tissue differentiation	
Vitamin B2 (Riboflavin)	• A factor in maintenance of good health	• Helps the body to utilize energy from food/ metabolize protein, fats and carbohydrates • Claim for specific population subgroups: -Additional amounts of Riboflavin are required during pregnancy and breast feeding when diet does not provide a sufficient daily intake	

Ingredients	Claims		
	General	Functional	Reduced Risk Reduction Claim
Vitamin B3 (Niacin)	• A factor in maintenance of good health	• Helps normal growth and development • Helps the body in utilization of energy from food	
Vitamin B5 (Panthothenic Acid)	• Helps in maintenance of good health	• Helps to metabolize fats and carbohydrates	
Vitamin B6 (Pyridoxine)	• A factor in maintenance of good health	• Helps the body to metabolize proteins, fats and carbohydrates	
Vitamin B12 (Cyanocobalamine)	• Helps in maintenance of good health	• Helps in the formation of red blood cell	
Vitamin C	• Helps in maintenance of good health	• For healthy bones, (cartilage), teeth, gums as well as general make-up of the body • Supports in immune health	
Vitamin D	• Maintenance of good health	• Helps in normal development and maintenance of bones and teeth • Helps the body utilize calcium and phosphorus • Claim for specific population subgroups: Elderly people who are confined indoors	

Ingredients	Claims		
	General	**Functional**	**Reduced Risk Reduction Claim**
Vitamin E	• Maintenance of good health		
Vitamin K	• Helps in maintenance of good health	• Support healthy bones	
Zeaxanthin	• Helps in maintenance of good health	• Support eye health	
Zinc	• A factor in maintenance of good health	• Helps to metabolize carbohydrates, fats and protein	

Notes:

1. *The claims listed above will serve as a guide for the applicant. Other wording that bring similar meaning may be considered*
2. *This list is not meant to be exhaustive and will be reviewed from time to time.*
3. *The Authority will nonetheless conduct a detailed evaluation of the evidence included in the report to ensure that the health claim is substantiated.*
4. *The Authority will be willing to consider review other than the listed above if the standards of evidence are consistent with those of the Authority.*
5. *All references must be current.*

APPENDIX 7

GUIDELINE ON REGISTRATION OF NATURAL PRODUCTS

IMPORTANT NOTES:

1. This part shall be read in conjunction with the relevant sections of the main DRGD.
2. Natural products shall be evaluated based on the criteria for safety and quality of the product, and where appropriate, efficacy/ claimed benefits.
3. This document is intended to provide guidance for the registration of natural products. However, this is a living document that is continually updated/ revised in the line with progress in scientific knowledge and experience.
4. The lists presented are by no means exhaustive. It may be reviewed as and when it is deemed necessary.

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1. GENERAL INFORMATION

1.1 DEFINITIONS

Natural products include traditional medicines, herbal products, homeopathic medicines and natural products with therapeutic claim.

1.1.1 Traditional medicine

As defined under the CDCR 1984, traditional medicine refers to any product used in the practice of indigenous medicine in which the drug consists solely of one or more naturally occurring substances of a plant, animal or mineral, of parts thereof, in the unextracted or crude extract form, and homeopathic medicine. It shall not include any sterile preparation, vaccine, any substance derived human parts, any isolated and characterized chemical substances.

1.1.2 Finished Herbal Product

Finished herbal products consist of herbal preparations made from one or more herbs. If more than one herb is used, the term "mixture herbal product" can also be used. Finished herbal products and mixture herbal products may contain excipients in addition to the active ingredients. However, finished products or mixture herbal products to which chemically defined active substance have been added, including synthetic compounds and/ isolated constituents from herbal materials, are not considered to be herbal.

1.1.3 Herbal Remedy

Herbal remedy refers to any drug consisting of a substance or a mixture of substances produced by drying, crushing or comminuting, but without subjecting to any other process, a natural substance or substances of plant, animal or mineral origin, or any part of such substance or substances.

1.1.4 Homeopathic Medicine

Homeopathic medicine refers to any pharmaceutical dosage form used in the homeopathic therapeutic system where diseases are treated by the use of minute amounts in which such substances are capable of producing in healthy persons symptoms similar to those of the disease being treated. Refer **Appendix 7A: Homeopathic Medicine**

1.1.5 Natural Products with Therapeutic Claim

Refer **Appendix 7B: Guideline on Natural Products with Therapeutic Claim**

1.2 EXEMPTIONS FROM PRODUCT REGISTRATION

The following preparations do not require registration with the Authority:

a) Extemporaneous preparation prepared and given directly to the patient by any traditional practitioner during the course of treatment;

b) Traditional preparation containing plants, animal parts or mineral substance or a mixture of these substances of natural origin that is produced only through drying, without any treatment/process involved. E.g. raw herbs;

c) Traditional preparation containing plants, animal parts, mineral substance/ extracts or a mixture of these substances of natural origin traditionally used as food, spices or flavouring of food that do not have any medicinal claim;

d) Traditional preparations used for cosmetic purposes, such as to whiten or improve the appearance of skin, hair, teeth, etc., have to be notified as cosmetic product.

1.3 PREPARATIONS NOT ALLOWED TO BE REGISTERED

a) Traditional preparation with the indication listed in "List of Non-Permissible Indications for Natural Product"

b) Traditional preparation containing herbal ingredients listed under Poisons Act 1952, except for those exempted for homeopathic preparation. Refer to Section 3.3 - General guidelines for the registration of homeopathic products.

c) Traditional preparation containing ingredient known or reported to cause any adverse effect on humans.

   Refer to List of Botanicals (& botanical ingredients) which are banned due to reported adverse event.

d) Traditional preparation containing combination of plants, animal parts or mineral substance of natural origin with chemical/ synthetic substance with therapeutic effect.

e) Traditional preparation containing combination of plants, animal parts or mineral substance of natural origin with vitamins and amino acids.

f) Traditional products are prohibited from containing ingredients derived from human origin. E.g.:

   i) CRINIS CARBONISATUS = Carbonised human hair
   (Reference: Pharmacopoeia of The People's Republic Of China: English Edition 1992)
   ii) HUMAN PLACENTA

1.4 CLASSIFICATION FOR SPECIFIC ACTIVE INGREDIENTS

1.4.1 PRODUCTS CONTAINING CASSIA/ SENNA:

Finished products containing cassia/ senna as an active ingredient with a daily dose of less than 0.5g of the crude drug or 20mg sennoside (standardized preparation) shall be classified as traditional products and restricted to traditional claims. Active ingredient consumed more than this daily limit will be classified as pharmaceutical product, depending on the product formulation.

1.4.2 PRODUCTS CONTAINING PSYLLIUM HUSK/ PLANTAGO OVATA

Finished products containing psyllium husk as an active ingredient and with a total daily consumption of less than 3.5g per day shall be classified as a non-drug. However, daily doses above this amount and up to 6.9g will require this product to be registered under the traditional product category.

Reference: Circular *Bil. (24) dlm.BPFK/PPP/07/11 Jld.5* *Pengkelasan Produk Mengandungi Psyllium Husk* (14 May 2010)

2. GENERAL REQUIREMENTS FOR REGISTRATION OF NATURAL PRODUCTS

2.1 PRODUCT NAME

a) If the product owner wishes to use a *formulary name, any amendments made to the product formulation such as the addition of active ingredients, removal of active ingredients or change in strength of active ingredients will not be permitted.

   * The name of the Chinese/ Ayurvedic proprietary medicine as stipulated in the reference such as Taiwan Pharmacopoeia, The Chinese Herbal Medicine Materia Medica, and Ayurvedic Pharmacopeia

b) A brand name added in front of the formulary name shall be required, in order to differentiate the product from products with the same formulary name.

c) Any product name that is the same or similar either in writing or pronunciation with the product name of an adulterated product is prohibited.

d) For a product name that is the name of active ingredient or a common name, e.g. *Kapsul Kacip Fatimah; Misal Kucing Tea*; Ortosiphon Capsule; Herbal Rub; Natural Herb Capsule, a brand name shall be added to the product name in order to differentiate and identify this specific product.

e) For single-ingredient products, in cases where the product name bears the name of the active ingredient, the strength should be added to the product name. E.g.: Sunsky Tongkat Ali 500 mg Capsule.

f) The dosage form is required to be added to the product name in the system (i.e in section A1)

g) Justification will be required to prove the "claim" made in the product name. E.g.: "Double Strength/ Acticoat/ WaterSol".

h) Product name supported by a registered trademark certificate will not be accepted if deemed inappropriate by the Authority or if it does not follow the regulations stated in this Appendix.

i) The replacement product may use the same product name as a previously registered product provided that the formulation (strength of active ingredient), product registration holder and dosage form of the product remain the same.

j) The name of the active ingredient is not allowed to be used as brand name.

k) The name of active ingredient combined with the product indication are not allowed to be used as product name.

l) Product names not permitted to be registered are specified in **Table 1** below:

Table 1: Non-Permissible Product Names

No.	Non-Permissible Product Names	Example
1.	**Prohibited use of disease names as stated in the Medicines (Advertisement and Sale) Act 1956 (Revised 1983)**	**Example:** Diabetes, Asthma, Cancer
2.	**Prohibited use of a single active ingredient as a product name in products containing more than one active ingredient unless product name contains words such as 'Plus, Compound, Complex, Herbanika**	**Example:** Tongkat Ali Capsule ---- But product contains tongkat ali, ginseng, ect.
3.	**Prohibited use of superlative - Names that indicates superiority in efficacy**	**Example:** Power/ Kuasa, Superior, Pure, Mustajab, Safe, Healthy/ Sihat, Penawar/ Shifa, VIP, Good, Heal/ Sembuh, Premium, Mustajab, Men/ Women/ Children Complete, Men/ Women/ Children Enriched, Paradise/ Syurga, Menawan, Booster

No.	Non-Permissible Product Names	Example
4.	**Prohibited use of spelling of words that may cause confusion** **Words that involve names of/ part thereof:** i) 20 disease names prohibited in the Medicines (Advertisement and Sale) Act 1956 (Revised 1983) ii) Diseases without scientific evidence of efficacy/ prescription medication to treat diseases/ parameters that indicate certain diseases (e.g. insulin, glucose) iii) Prohibited indication (e.g. to detoxify body)	**Example:** a) Go Out = GOUT b) UTix = Urinary Tract Infection c) Diabecine = Diabetes d) Metformon = Metformin e) Insuprem = Insulin f) Glucosey = Glucose g) DetoxB = Detox body
5.	**Prohibited use of names that may cause ambiguity** Ambiguous product name	**Example:** B For Energy?
6.	**Prohibited use of names that may be offensive or indecent**	**Example:** SENXBIG=SEnXBIG(label), Sexy, Enjoy, Paradise, Heavenly, Blue boy, Casanova, Desire *(Dezire), Sensual (Xenxual), Asmara, Syok*
7.	**Prohibited use of product names incoherent with the approved indication** Name containing a product claim whereas product is indicated for more than the approved indication	**Example:** Cough Syrup X= Approved indication for cough, dizziness, flu and itch
8.	**Prohibited use of product names that have elements of ludicrous belief** Statements referring to ancient believe/ negative spirits/ supernatural power	**Example:** Words such as miracle, magic, magical, miraculous, saintly, heavenly
9.	**Prohibited use of product names similar to the existing approved product names** Product names similar to the spelling and pronunciation of words of the existing product names	**Example:** Tenormin vs Tenormine vs Tenormy Re-Liv vs Re-Lif

No.	Non-Permissible Product Names	Example
10.	**Prohibited use of product names that may cause ambiguity in the nature of product (drug/ food/ beverage)** Product names similar to a food/ beverage product	**Example:** Juice, Health drink, Beverage, Kooky
11.	**Prohibited use of product names that represent professional advice or opinion or referring to the profession**	**Example:** Dr Sunny, Dr Noortier Rooibose Tea, Professor, Herbalist, Doctor
12.	**Prohibited use of product names that represent weight loss/ slimming properties/ names that can be associated with weight loss/ slim**	**Example:** Slim, Langsing, Trim, Trimnfit, *Sleen, Kurus, Susut perut, Xlim, Weight watcher, Burn*
13.	**Prohibited use of product names referring to any religious content**	**Example:** Maksum, Mahmudah, Arifbillah
14.	**Name of internal organ**	**Example:** Liver, Brain, Kidney, etc.
15.	**Use of abbreviation as a product name unless it carries no meaning**	**Example:** TB, UTI, HB, etc.
16.	**Other prohibited product names**	**Example:** Minda, IQ, Smart, Genius, Ultra Mega, Detox, Immune, Phase 2, Defense, Prime

Note:

1. This list is not meant to be exhaustive and will be reviewed from time to time.
2. The Authority reserves the right to disallow any other words or phrases for product names, which in its opinion, is misleading, improper or not factual.

2.2 INGREDIENTS

2.2.1 Active Ingredients

a) Active ingredients are substances that have a therapeutic role in the formulation. Substances included in the formulation as active ingredients must make a contribution to the proposed indications for the product. Where a claim links the presence of an ingredient to the product indication, that ingredient must contribute to that indication. The evidence may be scientific and or traditional.

b) Overages of active ingredient
Overages may be used during manufacture. An overage is where the amount of an ingredient added during manufacturing is greater than the nominated on the product label. Details of the overage used must be available.

c) Listed active ingredients can be checked through *https://www.npra.gov.my/* through "Product Search". Ingredients not listed will require safety and/or efficacy data evaluation prior to addition to this list.

d) For new active ingredients or new combination products, the following information shall be required:

- Product containing new single ingredient:

  i) Extract form

  - Information on the taxonomy of the ingredient;
  - Techniques and methods in preparing/ processing the extract and subsequently the product;
  - Information on the use and safety of the ingredient and the product quality standard.

  ii) Powder/ Granules

  - Information on the taxonomy of the ingredient;
  - Techniques and methods in preparing/ processing the extract and subsequently the product;
  - Information on the use and safety of the ingredient and the product.

- Product containing multiple ingredients (contains ingredients known to be used traditionally):

  - The source of the product formulation;
    e.g. Chinese Pharmacopoeia
  - Proof or evidence of the traditional use

- Product containing multiple ingredients (contains ingredients not known to be used traditionally):

  - Information on the use and safety of every new ingredient;
  - Safety data on the new formulation;
  - Regulatory status in other countries.

2.2.2 Premix

Effective from 1 December 2007, premixed ingredient(s) shall not be used in natural product (traditional) formulation,
Reference: Bil. (71) dlm. BPFK/02/5/1.3: Keputusan Mesyuarat PBKD: Larangan Penggunaan Bahan 'Premix' dalam Formulasi Produk Semulajadi (Tradisional) (1 June 2007)

2.2.3 Prohibited/ Banned Ingredients

The following lists present prohibited/banned ingredients not allowed in the formulation of natural products registered by the Authority:

A. Table 2 : Botanicals (and botanical ingredients) containing scheduled poisons listed under the Poisons Act 1952

B. Table 3 : Botanicals (and botanical ingredients) banned due to reported adverse event

C. Table 6 : Ingredients (botanicals and substance derived from animals) banned due to safety reasons

Table 2: Botanicals (and botanical ingredients) containing scheduled poisons listed under the Poisons Act 1952

Genus	Species	Common/ Local Name	Part of plant prohibited (whole plant unless otherwise specified)	Constituent(s) of concern
Aconitum	*All species*			Aconite
Asidosperma	*quebracho*	White quebracho		Asidospermine, yohimbine
Atropa	*belladonna*	Deadly nightshade		Atropine, hyoscine (scopolamine), hyoscyamine
Cabola	*albarrane*	Squill		Glycoside
Cannabis (controlled under Dangerous Drug Act 1952)	*All species*	Marijuana		Cannabinoids

Genus	Species	Common/ Local Name	Part of plant prohibited (whole plant unless otherwise specified)	Constituent(s) of concern
Catharanthus	*roseus*	Periwinkle Madagascar, Old Maid, *Vinca rosea,* Myrtle Syn: ***Vinca balcanica***, ***Vinca difformis***, ***Vinca heracea***, ***Vinca major***, ***Vinca minor***, ***Vincae minoris*** herba		Vinca, Vincristine, Vinblastine
Chondodendron	*tomentosum*	Curare, Velvet leaf, Ice Vine,		Tubocurarine
Claviceps	*purpurea*	Ergot		Ergometrine
Colchicum	*autumnale*	Autumn Crocus/ Meadow Saffron/ Naked Lady)		Colchicine
Datura	*metel*	Devil's Trumpet, Metel, J California Jimson Weed Syn.: *Datura wrightii*		Atropine, Scopolamine
Datura	*stramonium*	Jimson Weed/ Gypsum Weed,Loco Weed		Atropine, Hyoscyamine, Scopolamine
Delphinium	*staphysagria*	Lice bane, Stavesacre		Delphinine

Genus	Species	Common/ Local Name	Part of plant prohibited (whole plant unless otherwise specified)	Constituent(s) of concern
Digitalis	*purpurea*	Common Foxglove, Purple Foxglove, Kecubung	Leaf	Glycoside
Drimia	*maritima*	Squill Syn.:*Urginea maritima, Scilla maritima* Related substance: *Urginea indica, Urginea pancreatium, Urginea scilla*		Glycoside
Ephedra	All species	Ma Huang		Ephedrine, Pseudoephedrine
Gelsemium	*sempervirens*	Yellow Jessamine,Evening Trumpet,Carolina Jessamine		Gelsemine
Hyoscyamus	*muticus*	Egyptian henbane		Hyoscyamine
Hyoscyamus	*niger*	Black henbane		Hyoscyamine-atropine
Lobelia	*inflata*	Lobelia, pokeweed, Indian tobacco, gagroot, asthma weed, vomitwort, bladderpod,rapuntium inflatum.		Lobeline
Lobelia	*nicotianifolia*	Wild Tobacco		Lobeline

Genus	Species	Common/ Local Name	Part of plant prohibited (whole plant unless otherwise specified)	Constituent(s) of concern
Mitragyna	*speciosa*	Daun Ketum		Mitragynine
Nicotiana	*tabacum*	Common tobacco		Nicotine
Papaver	*somniferum*	Opium poppy		Morphine, codeine, hydrocodone, meperidine, methadone, papaverine
Pausinystalia	*yohimbe*	Yohimbe, Johimbe Syn. *Corynanthe johimbi,Corynanthe yohimbi*		Yohimbine
Physostigma	*venenosum*	Calabar bean		Physostigmine
Pilocarpus	*microphyllus*	Pilocarpus jaborandi, jaborandi		Pilocarpine
Punica	*granatum*	Pomegranate	Bark	Iso-Pellatrierine
Rauwolfia	*serpentina*	Indian snakeroot, Serpentine root		Reserpine
Rauwolfia	*vomitoria*	African serpentwood		Reserpine
Schoenocaulon	*officinale*	Veratrum officinale		Sabadilla, Veratrine
Scillae	*bulbus*	Sea onion, Squill		
Solanum	*nigrum*	Black nightshade		Solanine

Genus	Species	Common/ Local Name	Part of plant prohibited (whole plant unless otherwise specified)	Constituent(s) of concern
Strychnos	*nux-vomica*	Poison nut, Quaker button, strychnine tree, ma qian zi/maqianzi		Strychnine
Valerian	All species		All parts except for root part	Valepotriates
Veratrum	All species			
Vinca	All species	Including *Catharanthus roseus*		Vinca, Vincristine, Vinblastine, Vinpocetin

Table 3: Botanicals (and botanical ingredients) banned due to reported adverse event

Genus	Species	Common/ Local Name	Part of plant prohibited	Reason for prohibition
Aristolochia	*All species*			Contain **Aristolochic Acid** reported to cause kidney toxicity **(**Please refer to footnote below)**

Genus	Species	Common/ Local Name	Part of plant prohibited	Reason for prohibition
Berberis	*All species*			Berberine *Other herbs containing naturally-occuring berberine are allowed to be registered with specific requirements. Please refer to **Appendix 20**. Notes: Only prohibited for oral preparation.
Dioscorea	*hispida*	Ubi gadong, Gadong, Gadog, Gadong Lilin, Gadong Mabok, Ubi Arak, Ubi Akas, Taring Pelanduk, Susur Gadong, Gadongan, Kedut dan Ubi Bekoi	All parts	Contain dioscorine and dioscorinine reported to cause burning sensation in the throat, giddiness, followed by haematemesis, sensation of suffocation, drowsiness and exhaustion Not allowed for oral preparation
Drybalanops	*aromatica*	Borneo/ Malay/ Sumatra Camphor, Pokok Kapur	Whole herb	Contain camphor- not allowed for oral preparation
Borneolum	*syntheticum*	Bingpian, borneol		Contain borneol- not allowed for oral preparation

Genus	Species	Common/ Local Name	Part of plant prohibited	Reason for prohibition
Larrea	*tridenata*	Chapparal		Reported to cause liver toxicity
	mexicana			
Hydrastis	*canadensis*	Goldenseal, Eye Balm, Indian Dye		Reported to cause disturbance of the nervous system
Magnolia	*officinalis*	Houpu, Magnolia		Reported to cause kidney toxicity
Stephania	*tetrandra*			
Piper methysticum		Kava-kava		Reported to cause liver toxicity
Symphytum	*officinale*	Comfrey		
	asperum			
	x. uplandicum			
Senecio	*aureus*	Life root		
	jacobaea	Tansy ragwort, Tansy Butterweed		
	bicolor	Silver ragwort		
	nemorensis	Alpane ragwort, Wood ragwort		
	vulgaris	Common groundsel, Groundsel, Old-man-in the-spring		Reported to cause liver toxicity
	longilobus -*syn .with douglasii, filifolius*	Threadleaf groundsel, Threadleaf ragwort		

Genus	Species	Common/ Local Name	Part of plant prohibited	Reason for prohibition
	Scandens Buch.-Ham	German/African/Cape Ivy, Climbing Groundsel		

** To identify the botanicals that may contain Aristolochic Acid besides the Aristolochia genus, refer to:

a. **List A - Botanicals Known or Suspected to contain Aristolochic Acid (*Table 4*)**

b. **List B - Botanicals that may be Adulterated with Aristolochic Acid (*Table 5*)**

Notes:
Products containing any of the listed herbs (EXCEPT for Aristolochia spp. that is totally banned) will have to be sent to any governmental doping centre for testing and the result shall be attached with the registration form.

(Source for Lists A and B)

U. S. Food and Drug Administration

Center for Food Safety and Applied Nutrition

Office of Nutritional Products, Labeling, and

Health Supplements

[Revised April 9, 2001]

Table 4: List A: Botanicals Known or Suspected to Contain Aristolochic Acid

Botanical Name*	Common or Other Names
Asarum canadense Linn. Syn. Asarum acuminatum (Ashe) E.P. Bicknell Syn. Asarum ambiguum (E.P. Bicknell) Daniels Syn. Asarum canadense var. ambiguum (E.P. Bicknell) Farw. Syn. Asarum canadense var. reflexum (E.P. Bicknell) B.L. Rob. Syn. Asarum furcatum Raf. Syn. Asarum medium Raf. Syn. Asarum parvifolium Raf. Syn. Asarum reflexum E.P. Bicknell Syn. Asarum rubrocinctum Peattie	Wild ginger Indian ginger Canada snakeroot False coltsfoot Colic root Heart snakeroot Vermont snakeroot Southern snakeroot
Asarum himalaicum Hook. f. & Thomson ex Klotzsch or Asarum himalaycum Hook. f. & Thomson ex Klotzsch	Tanyou-saishin (Japanese)
Asarum splendens (F. Maek.) C.Y. Cheng & C.S. Yang	Do-saishin (Japanese)
Bragantia wallichii R.Br. Specimen exists at New York Botanical Gardens. Tropicos does not list this species as a synonym for any Thottea species. Kew Gardens Herbarium does not recognize the genera Bragantia. Until additional information is obtained we will use the name as cited in J. Nat. Products 45:657-666 (1982)	

Table 5: List B: Botanicals that may be Adulterated with Aristolochic Acid

Botanical Name*	Common or Other Names
Akebia spp.	Akebia Mu tong Ku mu tong Zi mutong Bai mu tong Mokutsu (Japanese) Mokt'ong (Korean
Akebia quinata (Houtt.) Decne. Syn. Rajania quinata Houtt.	Chocolate vine Fiveleaf akebia Mu tong Yu zhi zi Mokutsu (Japanese)
Akebia trifoliata (Thunb.) Koidz.	Mu tong Three leaf akebia Yu zhi zi
Asarum forbesii Maxim.	Batei-saishin (Japanese)
Asarum heterotropoides F. Schmidt Syn. Asarum heterotropoides F. Schmidt Syn. Asiasarum heterotropoides (F. Schmidt) F. Maek.	Keirin-saishin (Japanese) Chinese wild ginger Manchurian wild ginger Bei xi xin Xin xin

Botanical Name*	Common or Other Names
Asarum sieboldii Miq. Syn. Asarum sieboldii fo. seoulense (Nakai) C.Y. Cheng & C.S. Yang Syn. Asarum sieboldii var. seoulensis Nakai Syn. Asiasarum heterotropoides var. seoulense (Nakai) F. Maek. Syn. Asiasarum sieboldii (Miq.) F. Maek.	Usuba-saishin (Japanese) Chinese wild ginger Xi Xin Hua Xi Xin Manchurian wild ginger Siebold's wild ginger
Clematis spp.	Clematis Mufangji Clematidis Ireisen (Japanese) Wojoksum (Korean)
Clematis armandii Franch. Syn. Clematis armandii fo. farquhariana (W.T. Wang) Rehder & E.H. Wilson Syn. Clematis armandii var. biondiana (Pavol.) Rehder Syn. Clematis biondiana Pavol. Syn. Clematis ornithopus Ulbr.	Armand's clematis Chuan mu tong (stem) Xiao mu tong Armand's virgin bower
Clematis chinensis Osbeck.	Chinese clematis Wei ling xian (root)
Clematis hexapetala Pall.	
Clematis montana Buch.-Ham. ex DC. Syn. Clematis insulari-alpina Hayata	

Botanical Name*	Common or Other Names
Clematis uncinata Champ. ex Benth. Syn. Clematis alsomitrifolia Hayata Syn. Clematis chinensis var. uncinata (Champ. ex Benth.) Kuntze Syn. Clematis drakeana H. Lév. & Vaniot Syn. Clematis floribunda (Hayata) Yamam. Syn. Clematis gagnepainiana H. Lév. & Vaniot Syn. Clematis leiocarpa Oliv. Syn. Clematis ovatifolia T. Ito ex Maxim. Syn. Clematis uncinata var. biternata W.T. Wang Syn. Clematis uncinata var. coriacea Pamp. Syn. Clematis uncinata var. floribunda Hayata Syn. Clematis uncinata var. ovatifolia (T. Ito ex Maxim.) Ohwi ex Tamura Syn. Clematis uncinata var. taitongensis Y.C. Liu & C.H. Ou	
Cocculus spp.	Cocculus
Cocculus carolinus (L.) DC. Syn. Cebatha carolina Britton Syn. Epibaterium carolinum (L.) Britton Syn. Menispermum carolinum L.	
Cocculus diversifolius DC. Syn. Cocculus madagascariensis Diels	
Cocculus hirsutus (L.) Diels Syn. Cocculus villosus DC. Syn. Menispermum hirsutum L.	
Cocculus indicus Royle Syn. Anamirta paniculata Colebr.	Indian cockle
Cocculus laurifolius DC. Syn. Cinnamomum esquirolii H. Lév.	
Cocculus leaebe DC.	

Botanical Name*	Common or Other Names
Cocculus madagascariensis Diels Syn. Cocculus diversifolius DC.	
Cocculus orbiculatus DC. Syn. Cissampelos pareira Linn. Cocculus orbiculatus (L.) DC. Syn. Cocculus cuneatus Benth. Syn. Cocculus sarmentosus (Lour.) Diels Syn. Cocculus sarmentosus var. linearis Yamam. Syn. Cocculus sarmentosus var. pauciflorus Y.C. Wu Syn. Cocculus sarmentosus var. stenophyllus Merr. Syn. Cocculus thunbergii DC. Syn. Cocculus trilobus (Thunb.) DC. Syn. Menispermum orbiculatus L. Syn. Menispermum trilobum Thunb. Syn. Nephroia sarmentosa Lour.	Moku-boui (Japanese)
Cocculus palmatus (Lam.) DC.	Columba Columbo
Cocculus pendulus Diels Syn. Cebatha pendula (J.R. & C. Forst.) Kuntze Syn. Epibaterium pendulus Forst. f. Syn. Cocculus Epibaterium DC.	
Cocculus pendulus (Forst. & Forst.) Diels	
Cocculus palmatus Hook. Syn. Jateorhiza Miersii Oliver	Colombo
Cocculus thunbergii DC.	
Diploclisia affinis (Oliv.) Diels Syn. Diploclisia chinensis Merr. Syn. Cocculus affinis Oliv.	

Botanical Name*	Common or Other Names
Diploclisia chinensis Merrill	Xiangfangchi
Menispernum dauricum	
Saussurea lappa (Decne.) Sch. Bip. / Aucklandia Lappa	Mokkou (Japanese)
Sinomenium acutum (Thunb.) Rehder & E.H. Wilson Syn. Cocculus diversifolius var. cinereus Diels Syn. Cocculus heterophyllus Hemsl. & E.H. Wilson Syn. Menispermum acutum Thunb. Syn. Sinomenium acutum (Thunb.) Rehder & E.H. Wilson var. cinereum (Diels) Rehder & E.H. Wilson Syn. Sinomenium diversifolium (Diels) Diels	Orientvine Xunfengteng Dafengteng Daqingmuxinag Zhuigusan Da ye qingshener Mufangji Hanfangji Tuteng Zhuigufeng Maofangji
Stephania spp. (except for Stephania Tetrandra which is banned)	Stephania
Vladimiria souliei (Franch.) Ling	Sen-mokkou

Table 6: Ingredients (Botanicals and Substance Derived from Animals) banned due to safety reasons:

Genus	Species	Part of Plant/ Animal Prohibited *(whole plant/ animal unless otherwise specified)*	Constituent of Concern	Reasons for Prohibition
Abrus	*precatorius*	Seed	Abrin, Agrus, Agglutinin	- Potent inhibitor of protein and DNA synthesis - Severe diarrhea - Severe stomach cramp - Severe gastroenteritis
Adonis	*vernalis*		Adonitoxin	Uncontrolled dose can damage heart and cause death
Animal parts containing hormones (All species)				
Antiaris	*toxicaria*	Latex, sap	Cardiac glycoside (antiarin), Cardenolides & alkaloids with cardiac arresting potential	- Latex is highly poisonous - Paralyze heart muscle and cause death
Aristolochia	*All species*		Aristolochic acid	Reported to cause kidney toxicity, interstitial nephropathy
Calotropis	*gigantean*	Latex	Cardiac glycosides, calotropin	Severe mucous membrane irritation characterized by vomiting, diarrhea, bradycardia, convulsion and death
	procera			
Catharanthus	*roseus*		Vinca alkaloids	Bone marrow depression, central and peripheral (including autonomic) neurotoxicity

Genus	Species	Part of Plant/ Animal Prohibited *(whole plant/ animal unless otherwise specified)*	Constituent of Concern	Reasons for Prohibition
Cerbera	*manghas*	Seed	Digitoxynglycoside, Cerberine, Cerberoside, thevetin	- Drastic purgative and emetic - Burning in the stomach sensation, vertigo, nausea, violent purgation and colic - Heart failure
	odollam	Seed	Cerberine, Cerberoside, odollin, odolotoxin, thevetin and cerapain	- Gastro intestinal symptoms - cardiac toxicity - Nausea, severe retching, vomiting, abdominal pain, blurring of vision - Arterial block and nodal rhythm, hyperkalaemia - Irregular respiration, collapse and death from heart failure
Cinchona	*All species*		Quinine and derivatives	- Resistance of malarial vector - Use of bark is contraindicated in pregnancy and ulcers, intestinal or gastric, and if taken concomitantly with anticoagulants can increased their effects - Can elicit thrombocytopenia with purpura - Cinchona alkaloids are toxic. Can cause symptoms such as blindness, deafness, convulsions and paralysis

Genus	Species	Part of Plant/ Animal Prohibited *(whole plant/ animal unless otherwise specified)*	Constituent of Concern	Reasons for Prohibition
Citrullus	*Colocynthis*	Seed, fructus	Curcubitacin	- Carcinogenic effects, induce infertility in both sexes - Enterohepatonephro-toxicity
Dryopteris	*filix-mas*	Rhizome	Filicin, aspidinol	Hepatotoxic and blindness
Euphorbia	*antiquorum*	Latex	Apha euphorbol, Beta amyrin cycloartenol Euphol	Inflammation of the gastrointestinal mucous membrane, irritate skin, difficult respiration, eyes pupil dilated
	trigona			
Excoecaria	*agallocha*	Latex	Excoecaria phorbol	- Highly irritant to skin - Cause blindness if it enters the eye - Biocidal
Garcinia	*acuminate*	Gum resin	Cambogic acid, β-guttiferin, α-1 guttiferin	Vomiting, hypercarthasis, sympathetic irritation of sympathetic nervous system, caused death by gastro-enteritis
	hanburyi			
	morella			
Gelsemium	*elegans*	Root, leaf, rhizome	Gelsemine & gelseminine (Gelsemium indole alkaloid)	Paralysis, shortness of breath, muscle stiffeningcoma, hypocyclosis
Hyoscyamus	*muticus*		Hyoscyamine, atropine, hyoscine	Difficulty in swallowing and talking, transient bradycardia followed by tachycardia with palpitation and arrhythmias, CNS depression, coma

Genus	Species	Part of Plant/ Animal Prohibited *(whole plant/ animal unless otherwise specified)*	Constituent of Concern	Reasons for Prohibition
Jatropha	*multifida*	Fruit, seed	Phytotoxin (toxalbumin - Curcin	Nausea, vomiting, serious purgative action
Lantana	*camara*		Lantadene, Lancamaron	Cause toxicity in buffalo, cattle, sheep and goat. Symptoms include photosensitive dermatitis, jaundice and yellowing of mucous membrane and loss of appetite with a decrease in ruminal motility
Lobelia	*chinensis*		Lobeline	- Stimulant and has peripheral and central effects - Excessive use can cause nausea, vomiting and dizziness
	tupa			- Stimulant and has peripheral and central effects - Caused arrhythmias
Lytta	*vesicatoria*	Whole body, tincture	Cantharidin	- Excessive salivation, abdominal pain, swelling of kidney and urogenital system, headache, vomiting and diarrhea accompanied by bleeding - Burning of the mouth, dysphagia, nausea, hematemesis, gross hematuria and dysuria - Renal dysfunction and related to acute tubular necrosis and glomerular

Genus	Species	Part of Plant/ Animal Prohibited *(whole plant/ animal unless otherwise specified)*	Constituent of Concern	Reasons for Prohibition
				destruction
Melaleuca	*alternifolia*		Tea tree oil	Skin irritation, respiratory distress, vomiting, diarrhea and cytotoxic for oral administration. *** Banned in oral preparation**
Papaver	*All species*		Morphine and derivatives, codeine	- Potential abuse - Dependence, palpitation, hallucination, euphoric activities, CNS depression - Nervous system toxicity - Possible death from circulatory and respiratory failure
Pilocarpus	*pinnatifolius*	Bark	Pilocarpine	Bronchospasm, ocular problem, miosis, blurred vision
	jaborandi			
Podophyllum	*emodii*	Root, leaf	Podophyllin resin	- Serious systemic toxicity with excessive amounts (persistent nausea and vomiting, tachypnea, fever, stupor, coma, tachycardia, neuropathy and death) - Renal failure and hepatotoxicity
	peltatum			
Solanum	*dulcamara*	Leaf, flowering tops	Solanaceous alkaloids	Typical antimuscarinic effect e.g. dry mouth, mydriasis
Strophantus	*All species*		Strophantus alkaloids	Cardiac effect similar to digoxin

Genus	Species	Part of Plant/ Animal Prohibited *(whole plant/ animal unless otherwise specified)*	Constituent of Concern	Reasons for Prohibition
Symphytum	*pregrinum*		Pyrrolizidine alkaloid	Reported to cause liver toxicity

2.2.4 Use of Protected/ Endangered Ingredients

a) Protected/ Endangered Wildlife Species

It is the responsibility of the applicant to ensure that the ingredient(s) derived from wildlife species, its parts and derivatives used in the formulation **COMPLIES** with the Wildlife Conservation Act 2010 (Act 716) and International Trade in Endangered Species Act 2008 (Act 686). Both guidelines can be downloaded through the PERHILITAN website: *http://www.wildlife.gov.my.*

The applicant shall contact the following department to obtain the necessary permit/ license. A copy of the permit/ license shall be attached with the application form for product registration.

Department of Wildlife and National Parks, Peninsular Malaysia
Km. 10, Jalan Cheras,
56100 Kuala Lumpur,
Tel: +603-90866800, Fax: +603-90753873

b) Endangered Botanical Species

It is the responsibility of the applicant to declare the source of the botanical ingredient if it is listed under the International Trade in Endangered Species Act 2008 (Act 686). Please refer to *http://myphyto.gov.my* for the details.

2.3 EXCIPIENTS

a) Excipients are substances used to assist in the manufacture of active substance into dosage forms suitable for administration. Each excipient ingredient included in a formulation must have a justifiable excipient role and shall be controlled by specifications. The intended use of an excipient shall be appropriate.

b) New excipient will require safety and/or other additional data to support the function in the product prior to addition into the Quest database.

c) **LIST OF RESTRICTED EXCIPIENTS:**

Specific Excipient	Limits (Not allowed)
Menthol	- Oral (0 to 4mg/kg body weight/day) - External (>10%)

2.4 INDICATIONS

General note: *The indications listed below will serve as a guide for the applicant. For traditional/ homeopathic medicines, only low level claim(s) will be accepted. Other indication with the same level of claims may be considered if supported with traditional/ homeopathic use.*

2.4.1 Indications Acceptable for Natural Products

a) General Health Maintenance/ *Kesihatan Am*

"Traditionally used…./ *"Digunakan secara tradisional….*
"Homeopathically used.... / "*Digunakan secara homeopati*...

1. For general health/ for health/ *untuk kesihatan*.
2. For general health maintenance/ for general well-being/ *untuk mengekalkan kesihatan*
3. For health and strengthening the body/ *untuk kesihatan dan menguatkan badan*.
4. For relief of body heatiness/ *untuk melegakan panas badan*.
5. For general debility, weakness after illness or childbirth/ *untuk letih lesu/ kelesuan badan selepas sakit atau selepas bersalin.*
6. For loss of appetite/ *untuk kurang selera makan.*
7. For difficulty in sleep/ *bagi melegakan kesukaran untuk tidur.*
8. For relief of fatigue/ *untuk melegakan kepenatan.*
9. As an aid to overcome fatigue during physical exertion/ *membantu melegakan kepenatan fizikal.*
10. To expel wind and invigorate vital energy/ *untuk membuang angin dan menambah tenaga.*
11. To improve appetite/ *untuk menambah selera makan.*
12. For relieving waist ache and body weakness/ *untuk melegakan sakit pinggang dan lemah anggota badan.*
13. For relieving dizziness, sweating, and difficulty in sleep/ *untuk melegakan pening, berpeluh berlebihan dan sukar untuk tidur.*
14. For reducing body odour/ *untuk mengurangkan bau badan.*
15. For reducing toothache/ *untuk mengurangkan sakit gigi.*
16. To relieve tired eyes/ *untuk melegakan kepenatan mata.*
17. For healthy eyes/ *untuk kesihatan mata.*

b) Blood & Body Fluid/ *Darah & Cecair Badan*

"Traditionally used…./ *"Digunakan secara tradisional….*
"Homeopathically used.... / "*Digunakan secara homeopati*...

1. For improving blood circulation/ *untuk melancarkan perjalanan darah.*
2. To improve urination/ *untuk melawaskan kencing/ buang air kecil.*
3. For improving bowel movement/ *untuk melawaskan buang air besar.*
4. For relieving mild vomiting/ *untuk melegakan muntah ringan.*
5. For reducing minor swelling/ *untuk melegakan bengkak-bengkak ringan.*

c) Bone, Muscle & Joint/ *Tulang, Otot & Sendi*

"Traditionally used…./ *"Digunakan secara tradisional….*
"Homeopathically used.... / "*Digunakan secara homeopati*...

1. For strengthening muscle and bone/ *untuk menguatkan otot dan tulang.*
2. For relieving muscular ache/ *untuk melegakan sakit otot.*
3. For relieving waist ache and backache/ *untuk melegakan sakit pinggang dan sakit belakang.*
4. For relief of joints and muscular pain/ *untuk melegakan sakit sendi dan otot.*
5. For relieving muscles sprain/ *untuk melegakan terseliuh/ terkehel.*

d) Pain & Fever/ *Sakit Am & Demam*

"Traditionally used…./ *"Digunakan secara tradisional….*
"Homeopathically used.... / "*Digunakan secara homeopati*...

1. To relieve/ alleviate pain/ *untuk melegakan kesakitan.*
2. For relieving fever/ *untuk melegakan demam*.
3. For relieving headache/ *untuk melegakan sakit kepala.*
4. For relieving pain and itchiness related to piles/ *untuk melegakan kesakitan dan rasa gatal akibat buasir.*
5. For symptomatic relief of body heatiness/ body heat / *untuk melegakan panas badan.*

e) Cough & Cold/ *Batuk & Selsema*

"Traditionally used……/ *"Digunakan secara tradisional…..*
"Homeopathically used.... / "*Digunakan secara homeopati*...

1. For relief of fever, cough and cold/ *untuk melegakan demam, batuk dan selsema.*
2. For relief of sore throat/ *untuk melegakan sakit tekak.*

3. For reducing phlegm and relief of cough, sore throat and body heatiness/ *untuk mengurangkan kahak dan melegakan batuk, sakit tekak dan panas badan.*
4. For relief of throat irritations and cough/ *untuk melegakan sakit tekak dan batuk.*
5. For relief of nasal congestion/ *untuk melegakan hidung tersumbat.*
6. For relief of sore throat and cough/ *untuk melegakan sakit tekak dan batuk.*
7. For relief of mouth ulcers due to heatiness/ *untuk melegakan sakit mulut akibat panas badan.*
8. To relieve sinusitis/ *untuk melegakan resdung.*

f) Digestive System/ *Sistem Pencernaan*

"Traditionally used…./ *"Digunakan secara tradisional….*
"Homeopathically used.... / "*Digunakan secara homeopati*...

1. For relief of stomach ache, mild diarrhoea/ *untuk melegakan sakit perut, cirit-birit ringan.*
2. For relief of flatulence, stomach ache, mild diarrhoea, and loss of appetite/ *untuk melegakan kembung perut, sakit perut, cirit-birit ringan dan kurang selera makan.*
3. For relief of mild diarrhoea, vomiting and improve appetite/ *untuk melegakan cirit-birit, muntah ringan dan menambah selera makan.*
4. For relief of mild constipation/ *untuk melegakan sembelit ringan.*
5. To improve appetite and digestion/ *untuk menambah selera makan dan pencernaan.*
6. For relieving abdominal pain and flatulence/ *untuk melegakan sakit perut dan kembung perut.*
7. For relief of stomach ache, constipation, mild vomiting and indigestion/ *untuk melegakan sakit perut, sembelit, muntah ringan dan makanan tidak hadam*.
8. Aid in digestion/ *untuk membantu penghadaman.*

g) Women's Health/ *Kesihatan Wanita*

"Traditionally used…../ *"Digunakan secara tradisional….*
"Homeopathically used.... / "*Digunakan secara homeopati*...

1. To relieve menstrual pain, headache and to regulate menstruation/ *untuk melegakan senggugut, sakit kepala dan melancarkan perjalanan haid.*
2. To reduce body weight/ *untuk mengurangkan berat badan.*
   *[**Note:** For specific active ingredient only supported by established reference, examples: Cassia species, Garcinia Cambogia and Phaseolus vulgaris]*
3. For relief of vaginal discharge/ *untuk melegakan keputihan.*
4. For women after childbirth/ *untuk wanita lepas bersalin.*
5. For general wellbeing and strengthen the body after childbirth/ *untuk kesihatan dan menguatkan badan wanita selepas bersalin.*
6. For women after childbirth to reduce body weight/ *untuk ibu-ibu selepas bersalin mengurangkan berat badan.*

7. For symptomatic relief of vaginal discharge and mild itch/ *untuk melegakan keputihan dan gatal-gatal ringan.*
8. To improve menstrual flow, for relief of menstrual pain, vaginal discharge and flatulence/ *untuk melancarkan haid, melegakan senggugut, keputihan dan kembung perut.*
9. For strengthening body muscle and reducing body weight/ *untuk menguatkan otot-otot tubuh dan mengurangkan berat badan.*
10. For general health of women after childbirth/ *untuk menyihatkan rahim selepas melahirkan anak.*
11. To relieve symptoms of menopause/ *untuk melegakan simptom menopause. [**Note:** For specific active ingredient only supported by established reference, examples: red clover (trifolium pratense) and black cohosh (cimicifuga racemosa)]*

h) Men's Health/ *Kesihatan Lelaki*

"Traditonally used…./ *"Digunakan secara tradisional….*
"Homeopathically used.... / "*Digunakan secara homeopati*...

1. For men's health and energy/ for vitality/ *untuk memulihkan tenaga dan kesihatan lelaki.*

i) Skin And External Usage/ *Kulit Dan Kegunaan Luar*

"Traditionally used…../ *"Digunakan secara tradisional…*
"Homeopathically used.... / "*Digunakan secara homeopati*...

1. For symptomatic relief of pain and itch associated with insect bites/ *untuk melegakan sakit dan gatal-gatal digigit serangga.*
2. For relief of minor burns/ *untuk melegakan lecur ringan.*
3. For relief minor cuts/ *untuk melegakan luka-luka ringan.*
4. For relief of minor bruises/ *untuk melegakan lebam yang ringan.*
5. For reducing pimples/ *untuk mengurangkan jerawat.*
6. To help maintaining healthy skin, nail and hair/ *untuk kesihatan kulit, kuku dan rambut.*
7. For reducing pimples and mild itch/ *untuk melegakan jerawat dan gatal-gatal ringan.*

2.4.2 Non-Permissible Indications

Table 7:

NO.	NON-PERMISSIBLE INDICATIONS
1.	*Penyakit atau kecacatan ginjal* / Disease or defects of the kidney
2.	*Penyakit atau kecacatan jantung* / Disease or defects of the heart
3.	*Kencing manis* / Diabetes
4.	*Epilepsi atau sawan* / Epilepsy or fits
5.	*Kelumpuhan* / Paralysis
6.	*Tibi* / Tuberculosis
7.	*Asma* / Asthma
8.	*Kusta* / Leprosy
9.	*Kanser* / Cancer
10.	*Kepekakan* / Deafness
11.	*Ketagihan dadah* / Drug addiction
12.	*Hernia atau pecah* / Hernia or rupture
13.	*Penyakit mata* / Disease of the eye
14.	*Hipertensi (Darah Tinggi)* / Hypertension
15.	*Sakit otak* / Mental disorder
16.	*Kemandulan* / Infertility
17.	*Kaku* / Frigidity
18.	*Lemah fungsi seks atau impoten* / Impairment of sexual function or impotency
19.	*Penyakit venerus* / Venereal disease
20.	*Lemah urat saraf atau aduan atau kelemahan lain timbul daripada atau berhubung kait dengan perhubungan seks* / Nervous debility or pother complaint of infirmity arising from or relating to sexual intercourse.

2.5 PARTICULARS OF PACKING

- The maximum pack size allowed for all dosage forms is based on the daily dosing for a quantity not exceeding six (6) months usage.
- Packaging particulars to the listing of packing are:

  C1: Pack size and fill details by weight, or volume or quantity.

  C2: Container type

  C3: Barcode/ serial number (optional)

  C4: Recommended distributor's price (optional)

  C5: Recommended retail price (optional)
- Measuring spoon/ device must be provided for all products in bulk powder form, unless if for physician use only.
- Sample pack size should not exceed 20 capsules/ tablets.

2.6 LABELLING REQUIREMENTS

a) The following information shown in **Table 8** below shall be included in the product label.

No.	Items	Immediate Label	Outer Label	Package Insert	Blister Pack
1.	Product name	√	√	√	√
2.	Dosage Form	√	√	√	√
3.	Name of active ingredients, including part of plant used	√	√	√	
4.	Strength of active ingredient in weight	√	√	√	
5.	Indication	√	√	√	
6.	Batch number	√	√		√
7.	Manufacturing date	√	√		
8.	Expiry date	√	√		√
9.	Dosage/ Use instruction	√	√	√	
10.	Storage condition(s) - state temperature used in the stability study - state "Protect from light and moisture" (If product is not packed in moisture resistant container)	√	√	√	
11.	Registration number (MAL)	√	√		√
12.	Name and address of product registration holder (Example: Product Registration Holder: XXXXX)	√	√	√	

No.	Items	Immediate Label	Outer Label	Package Insert	Blister Pack
13.	Name and address of manufacturer (Example: Manufacturer: XXXXX)	√ At least name of town/ city and country of manufacturer	√ At least name of town/ city and country of manufacturer	√	
14.	Warning label (if applicable) e.g. Ginseng, Bee Pollen etc. as required under 2.6.2 Specific Labelling Statements/ Warning & Precautions *Note: Please refer to* **Appendix 19: General Labelling Requirements** **Appendix 20: Specific Labelling Requirements**	√	√	√	
15.	Pack size (unit/ volume)	√	√	√	
16.	Name and strength of preservative	√	√	√	
17.	Name and content of alcohol, where present	√	√	√	
18.	To declare source of ingredients derived from animal origin (active and excipient) including starting materials and gelatine (capsule shell).	√	√		
19.	Additional statement (if applicable)	√	√	√	
20.	Contraindication/ Precaution (if any)	√	√	√	
21.	Security Label (Hologram) # In products without an outer carton, the security label shall be applied onto the immediate label. The security label shall not be applied onto the outer shrink		√ #		

No.	Items	Immediate Label	Outer Label	Package Insert	Blister Pack
	wrap of the product.				
22.	Product Description			√	
23.	Date of Revision			√	

b) All labels and package inserts must be in *Bahasa Malaysia* or English. Additional translation to another language will be allowed.

c) Font size of the product name on the label, including alphabets and numbers, should be equal in size.

d) For a product containing two (2) or more active ingredients, the font size of each active ingredient highlighted on the inner/ outer carton must be of equal size and equal prominence (Note: This does not refer to the product name, but the statement made on the label). Justification for highlighting certain ingredients only on the product name/ label must be provided and is subject to approval by the Drug Evaluation Committee.

e) All the following requirements must be stated on the labels and package inserts:

- State the weight per dosage form
- State the quantity/ content of active ingredients per dosage form
- For products in liquid form (syrup), content of active ingredients shall be stated as follows:

  "Each ___ml (per dosage) product contains extract of the following ingredients"

  Herb X = ___mg

  Herb Y = ___mg
- Check and correct all spelling/ grammar and translations.

f) For products meant for traditional practitioner/ physician use, state its primary use by the related traditional physician/ practitioner on the label.

E.g.: 'For Chinese Physician Use Only' OR
'For Ayurvedic Practitioner Use Only'.

g) **Example of label approved by the Authority**:

This is a traditional medicine

Please consult your pharmacist/ doctor before taking this product

Jauhkan daripada capaian kanak-kanak
Keep out of reach of children

Indication: Traditionally used for women's health

Warning: Pregnancy and breastfeeding: Insufficient reliable data

Keep below 30 ° celcius
Protect from light and moisture

Batch No.:
Manufacturing date:
Expiry date:

KAPSUL PQR
500MG

MALXXXXXXXXT

50 CAPSULE

Hologram

Each Capsule (Vegetable capsule) contains :

Folium XX 200mg
Fructus QY 300mg

Dosage
Adult : 2 capsules taken twice a day after food

Product Registration Holder:
Syarikat XYZ Sdn Bhd
18, Jalan Utama
47000 Sungai Buloh
Selangor

Manufactured by:
Syarikat ABC Sdn Bhd
3, Jalan Universiti
46730 Petaling Jaya
Selangor

2.6.1 Statements to Be Stated on Product Label

The following statements shall also be stated on the product label, where applicable:

- For product with an indication "For general health/ well-being" **or** "*Untuk kesihatan umum*":
  - "Please consult your pharmacist / doctor before taking this product **or** *Sila merujuk kepada ahli farmasi/ doktor sebelum mengambil produk ini."*

- For product with an indication "To relieve symptoms for…. (any illness)" **or** "*untuk mengurangkan tanda-tanda/ simptom….*":
  - "Please consult your pharmacist/ doctor if symptoms persist/ worsen **or** *Sila merujuk kepada ahli farmasi/ doktor jika simptom berlarutan/ bertambah teruk."*

- For product with indication "To regulate menstruation/ To improve menstrual flow":
  "Contraindicated in pregnant women."

- For product with indication 'To reduce body weight', state these statements, (unless proven otherwise):
  - **"Balanced diet and regular exercise are essential."**
  - **"Safety on long term use has not been established."**

- "This is a traditional medicine/ *Ini adalah ubat tradisional*." **OR** "This is a homeopathy medicine/ *Ini adalah ubat homeopati."*

- Unless otherwise supported, all natural products label shall state the following general cautionary statement, **EXCEPT** for products with indication for men's health or product for children use only:

  "Pregnancy and breastfeeding: Insufficient reliable data"

- For product with an indication to be taken/ used **specially for women,** refer to **2.6.3 Cautionary Statement for Products Specially Used in Women.**

- "Keep out of reach of children & *Jauhkan daripada capaian kanak-kanak"* (in both *Bahasa Malaysia* and English).

- "Protect from light and moisture."

- State the storage condition according to the temperature stated in stability data.

- For products containing <u>ingredients</u> as specified below, include the required statements:

  i) **Animal part(s):**
  "This product contains animal part(s)."

  ii) **Animal origin(s):**
  Example: for active ingredients such as pearl, shell of oyster (Concha), etc.
  "This product contains substance(s) from animal origin."

  iii) **Porcine:**
  "This product contains animal part(s) (porcine/ pig)."

  iv) **Alcohol:**
  - "This product contains alcohol."
  - Please declare the percentage of alcohol contained in the product.

- For the following <u>dosage forms</u>, include:

  i) **Topical preparations:** "For external use only."

  ii) **Liquids and suspensions:** "Shake well before use"

- Labels with the picture/ graphic of the herb/ animal should not have the picture/ graphic of only one (1) particular active ingredient if the product formulation contains more than one (1) ingredient. For multiple ingredients exceeding two (2), the label should have picture/ graphics of at least two (2) ingredients on the label.

- Any special/ specific name of active ingredient/ extract stated on the label should be positioned away from name of the active ingredient in the product formulation.

- Any picture of the founder placed on the label must be decent and should not exceed 1/10th of the panel.

2.6.2 Specific Labelling Statements/ Warning & Precautions

- Refer to **Appendix 20: Specific Labelling Requirements** for common substance (e.g. alfalfa, bee pollen, black cohosh etc.).
- For products containing the following substances, specific cautionary statement as specified shall be included:

No.	Substance	Specific Cautionary Statement
1.	For product containing **'Anti-diarrhoea'**, please state:	**"Contraindicated in children below 1 year old" (to be stated for products with children dosing only)**
2.	For product containing **Benzyl Alcohol/ Phenylmethanol (as preservative)**, please state:	**As this preparation contains benzyl alcohol, its use shall be avoided in children under 2 years of age. Not to be used in neonates.**
3.	For products containing **Camphor**:	i) The following warning shall be stated on the label: **WARNING:** **CAN CAUSE CONVULSION** **CONTRAINDICATED IN CHILDREN BELOW 2 YEARS OF AGE.** **CAUTION MUST BE EXERCISED WHEN OLDER CHILDREN ARE TREATED.** **AVOID DIRECT APPLICATION INTO NOSTRILS** **PRECAUTION:** It is dangerous to place any camphor – containing product into the nostril of children. A small amount applied this way may cause immediate collapse. - Avoid contact with the eyes. - Do not apply to wounds or damaged skin. ii) The following warning and precaution shall be stated on product leaflet: **WARNING: "This product is contraindicated in children under 2 years of age. Caution must be exercised when older children are treated."**

No.	Substance	Specific Cautionary Statement
		PRECAUTION: "It is dangerous to place any camphor containing product into the nostrils of children. A small amount applied this way may cause immediate collapse."
4.	For pack size meant as samples, please state:	**Sample not for sale**

2.6.3 Cautionary Statements for Products Specifically Used in Women

Special precaution shall be given to ingredients taken during pregnancy. The Authority urges pregnant women to consult their medical/ traditional health care providers prior to taking any natural products.

Unless otherwise supported, all natural products label shall state the following general cautionary statement:

"Pregnancy and breastfeeding: Insufficient reliable data"

However, for products containing any ingredients as listed in the following lists, i.e. List of Prohibited Ingredients in Pregnancy and List of Restricted Ingredients in Pregnancy, the following cautionary statement shall be stated in the product label:

i) Prohibited Ingredients in Pregnancy:
"Contraindicated in pregnant women. Insufficient reliable data in breastfeeding women"

ii) Restricted Ingredients in Pregnancy:
"To be used with caution in pregnancy. Insufficient reliable data in breastfeeding women"

The following list has been compiled based on well documented information as an aid to the industry to comply with the labelling requirement for products used during pregnancy.

Table 9: List of Prohibited Ingredients in Pregnancy

	Latin Compendium Name	Common/ Chinese Name	Remarks
A	Acorus Calamus	Calamus	
	Achillea Millefolium	Yarrow	
	Aloe barbadensis	Aloe vera	
	Angelica Archangelica	Angelica	
	Angelica sinensis	Dong Quai	When taken orally
	Artemisia Vulgaris	Mugwort	
	Arctostaphylos Uva Ursi	Uva Ursi	
	Artemisia Absinthium	Wormwood	
	Astragalus gummifer	Tragacanth	
B	Bryonia Alba	White Bryony	
	Bupleurum chinense, Bupleurum falcatum	Bupleurum	
C	Calendula Officinalis	Calendula	
	Calomel (mercurous chloride; Hg_2Cl_2)	Qing fen	
	Capsella Bursa-Pastoris	Shepherd's Purse	
	Cassia Marilandica	Senna	
	Caulophyllum Thalictroides	Blue Cohosh	When taken orally
	Chamaemelum nobile (Anthemis nobilis)	Roman Chamomile	When taken orally
	Chenopodium Ambrosioides	Epazote	
	Cichorium intybus	Chicory	
	Cimicifuga Racemosa	Black Cohosh	When taken orally
	Cnicus Benedictus	Blessed Thistle	
	Conium maculatum	Hemlock	
	Convalaria Majalis	Lily of the Valley	
	Cortex Cinnamomum Cassia	Rou Gui	
	Cortex Moutan Radicis	Mu Dan Pi	
	Crocus Sativus	Saffron	

	Latin Compendium Name	Common/ Chinese Name	Remarks
	Croton tiglium	Ba dou	
E	Epimedium grandiflorum	Horny goat weed	
	Equisetum arvense L.	Horsetail	
F	Flos Carthamus Tinctorius	Hong Hua	
	Flos Daphne Genkwa	Yuan Hua	
	Folium Cassia Angustifolia	Fan Xie Ye	
	Fructus Citrus Aurantium	Zhi Ke	
	Fructus Aurantii Immaturus	Zhi Shi	
G	Gentiana lutea	Gentian	
	Ginkgo Biloba	Ginkgo	
	Glycyrrhiza glabra/ Glycyrrhiza uralensis	Licorice	
H	Helleborus spp.	Hellebore	
	Hyssopus officinalis	Hissopo	
I	Iris Versicolor	Blue Flag	
	Ipecac Ipecachuana	Ipecac	
J	Juglans Canadensis	Butternut	
	Juglans nigra	Black Walnut	
	Juniper (***Juniperus communis)***	Juniper Berries	
L	Leonurus Cardiaca	Motherwort	
M	Marrubium Vulgare	Horehound	
	Mentha Pulegium	Pennyroyal	When used orally or topically
	Monarda didyma	Bee Balm	
	Moschus berezovskii Flerov, Moschus sifanicus Przewalski, Moschus moschferus Linnaeus (Moschus)	She xiang / musk	
	Mylabris / Radix Sacchari Arundinacei	Ban Mao	
N	Natrii Sulfas	Mang Xiao	

	Latin Compendium Name	Common/ Chinese Name	Remarks
	Nepeta cataria	Catnip	
	Nigella sativa	Black seed/ black cumin	
O	**Oenothera biennis** *L.*	Evening Primrose	
P	Panax Ginseng, Panax Quinquefolius	Ginseng	
	Passiflora incarnata *L.*	Passion Flower	When taken orally
	Petroselinum Crispum	Parsley	
	Podophyllum Peltatum	American Mandrake	
	Polygala Senega	Senega Snakeroot	
R	Radix Euphorbiae Pekinensis	Jing Da Ji	
	Radix et Rhizoma Rheum Palmatum	Da Huang	
	Radix Kansui/ Radix Euphorbiae Kansui	Gan Sui	
	Radix Phytolacca actinosa	Shang Lu	
	Rhizoma Sparganium Stoloniferum	San Leng	
	Resina Toxicodendri/ Resina Rhois Praeparata	Gan Qi	
	Rhizome et Radix Veratrum nigrum L.	Li Lu	
	Radix Achyranthis Bidentatae	Niu Xi	
	Rhizoma Ligustici Chuanxiong	Chuan Xiong	
	Rhizome Curcumae Longae	Jiang Huang	
	Rhamnus Purshiana	Cascara Sagrada	
	Rhamnus Frangula	Buckthorn	
	Rheum Palmatum	Rhubarb Root	
	Ruta Graveolens	Rue	
	Rheum Australe	Turkey Rhubarb	
S	Sanguinaria Canadensis	Bloodroot	
	Semen Pharbitis nil	Qian Niu Zi	

	Latin Compendium Name	Common/ Chinese Name	Remarks
	Semen Strychnos nux-vomica. L.	Ma Qian Zi	
	Semen Prunus Persica	Tao Ren	
	Serenoa repens	Saw Palmetto	When taken orally
T	Tabebuia impetiginosa	Pay D' Arco	When taken orally
	Tanacetum parthenium	Feverfew	
	Tanacetum Vulgare	Tansy	
	Thuja Occidentalis	Arbor Vitae	
	Turnera Diffusa	Damiana	
	Trigonella foenum-graecum	Fenugreek	
	Trillium Erectum	Bethroot	
	Tussilago Farfara	Coltsfoot	
V	Venenum Bufonis	Chan Su	
	Viscum Album	European Mistletoe	
W	Whitmania pigra Whitman, Hirudo nipponica Whitman, Whitmania acranulata Whitman (Hirudo)	Shui Zhi	
X	Xanthoxylum Americanum	Prickley Ash	

Note: The list is not to be exhaustive and will be reviewed from time to time.

Table 10: Restricted in Pregnancy

No.	Latin Compendium Name	Common/ Chinese Name	Remarks
1.	Zingiber Officinalis	Ginger	> 1g dry weight/day

Note: The list is not to be exhaustive and will be reviewed from time to time.

2.6.4 Prohibited Visual/ Graphics/ Statement on Packaging Materials (Label, Box, Package Insert or Consumer Medication Information Leaflet)

General requirements:

- The label should not contain any statement or visual presentation which, whether directly or by implication, is likely to mislead the consumer about any product.
- The graphics printed on the outer and inner labels have to be standardized to avoid confusion to the customers.

Table 11:

No.	Subject Matter	Example(s)	Notes
1.	Marketing strategy	**Example:** "Money back guarantee" "Buy 1 free 1" "Backed by RM5 million product Liability Insurance"	Such statements are prohibited on labels.
2.	Usage guide that promotes use of other product(s)	**Example:** "After consumption of this product (Product A), for better results, it is recommended to take Product B"	Not allowed
3.	Consumer testimonial		Prohibited on product label

No.	Subject Matter	Example(s)	Notes
4.	Clinical Trial results or any information on clinical trial done on product	Example: "Clinically Tested" "Randomized Double-Blind Placebo Control Clinical Study"	Such statements are prohibited on labels.
5.	Opinion/ Name of prominent figure(s)/ professionals on product or its active ingredient/ content	**Example:** Opinion of product/ formulation inventor	Prohibited on product label
6.	Label design (graphic and color) similar to labels from another company		Prohibited on product label
7.	Statement on herbal origin	**Example:** Source from the Mountains of Alps	Allowed if proven true
8.	Introduction/ description of founder/ manufacturer/ professionals, i.e. elaboration on the identity of the founder or manufacturer	**Example:** "Manufacturer ABC is a GMP certified manufacturer and has manufactured many products." "Founder Dr. ABC is a world renowned surgeon."	Prohibited on product label

No.	Subject Matter	Example(s)	Notes
9.	Logo with certification	**Example:** SIRIM/ ISO / GMP /HACCP	Prohibited on product label because certification renewal is on a yearly basis
10.	Name/ Statement / Logo/ registered trademark that does not satisfy the specifications of the Traditional Unit	**Example:** "Dr. ABC's Formula" "Nothing like it"	Prohibited on product label
11.	Special technique used/ superiority in ingredients	**Example:** Capsule coat	Allowed if proven true
12.	Nutritional claims with analysis certificate attached	**Example:** Calorie, Fat, Protein and others	Prohibited on product label This is not a food supplement.
13.	Graphics or picture of internal organs	**Example:** Kidney, Heart, Nerves.	Prohibited on product label
14.	Photograph of celebrities	**Example:** Artiste, Sports person(s), Politician	Prohibited on product label
15.	Gender symbol (male or female)	(♀ and / or ♂)	Prohibited on product label

No.	Subject Matter	Example(s)	Notes
16.	Indecent photographs/ pornography/ graphics/ images		Prohibited on product label
17.	Graphics incoherent with the indication	**Example:** - Noted indication is for constipation, but graphics on label shows a slim-looking lady which denotes indication for weight loss - Indication for urination but label graphics contains picture of a water hose.	Prohibited on product label
18.	Highlighting unnecessary body parts	**Example:** Indication is for general health but graphics on label highlights male and female sexual organ parts	Prohibited on product label
19.	Graphics of plants or animal that may cause confusion	**Example:** Radix Ginseng which is improvised as a male sexual organ	Prohibited on product label

No.	Subject Matter	Example(s)	Notes
20.	Statement on sugars in traditional products	**Example:** - This product contains no added sugar	Allowable on product label provided the product contains no fructose, glucose, sucrose or other kind of sugars with a potential to affect diabetics are not included in the formulation
21.	Negative statements	**Example:** - No active ingredient - No gluten, yeast, etc.	Prohibited on product label
22.	Other statements	**Example:** - This product is blended with premium quality - Certified chemical residue free	Prohibited on product label
23.	Label design (graphic/ colour) similar to/ same as an adulterated product		Prohibited on product label

Notes:

1. *This list is not meant to be exhaustive and will be reviewed from time to time.*
2. *The Authority reserves the right to disallow any other words, phrases or graphics for product label, which in its opinion, is misleading, improper or not factual.*

2.7 QUALITY CONTROL

2.7.1 Quality Testing for Specific Ingredient

i) For product containing Aphanizomenon flosaquae, applicants shall provide certificates of analysis showing that the microcystin-LR or total microcystins content of the raw material does not exceed 1µg/g and the finished product has been tested for microcystin-LR using an acceptable method;

ii) For products containing Red Yeast Rice (*Monascus purpureus*), applicants shall provide certificates of analysis (for both raw material and finished product) showing the Monacolin-K content. The percentage of Monacolin-K shall not exceed 1% and the Monakolin-K consumed shall not exceed 10 mg per day.

2.7.2 Limit Test for Heavy Metals

Limit for heavy metals:

i)	Lead	:	NMT 10.0 mg/kg or 10.0 mg/litre (10.0ppm)
ii)	Arsenic	:	NMT 5.0 mg/kg or 5.0 mg/litre (5.0ppm)
iii)	Mercury	:	NMT 0.5 mg/kg or 0.5 mg/litre (0.5ppm)
iv)	Cadmium	:	NMT 0.3 mg/kg or 0.3 mg/litre (0.3ppm)

2.7.3 Disintegration Test

Disintegration time **for tablets, capsules and pills**

i)	Uncoated tablets	:	NMT 30 minutes
ii)	Film-coated tablets	:	NMT 30 minutes
iii)	Sugar-coated tablets	:	NMT 60 minutes
iv)	Enteric-coated tablets	:	Does not disintegrate for 120 minutes in acid solution but to disintegrate within 60 minutes in buffer solution
v)	Capsules	:	NMT 30 minutes
vi)	Pills	:	NMT 120 minutes

2.7.4 Test for Uniformity of Weight (For Tablets and Capsules Only)

i) Tablet

- For tablet with average weight of 130mg or less: Not more than 2 tablets differ from the average weight by more than 10% AND no tablets differ from the average weight by more than 20%
- For tablet with average weight between 130-324mg: Not more than 2 tablets differ from the average weight by more than 7.5% AND no tablet differs from the average weights by more than 15%
- For tablets with average weight more than 324mg: Not more than 2 tablets differ from the average weight by more than 5% AND no tablet differs from the average weight by more than 10%

ii) Capsule

Individual weight of the capsule to be within the limit of 90 - 110% of the average weight.

2.7.5 Tests for Microbial Contamination

A. Herbal medicinal products containing herbal drugs, with or without excipients, intended for the preparation of infusions and decoctions using boiling water (e.g. herbal teas, with or without added flavourings)

Microbiological Quality	Acceptance Criteria
TAMC	NMT 5 x 10^7 CFU/g
TYMC	NMT 5 x 10^5 CFU/g
Escherichia coli	NMT 1 x 10^3 CFU/g
Salmonella	Absence (25 g)

B. Herbal medicinal products containing, e.g. extracts and/or herbal drugs, with or without excipients, where the method of processing (e.g., extraction) or, where appropriate, in the case of herbal drugs, of pre-treatment reduces the levels of organism to below those stated for this category

Microbiological Quality	Acceptance Criteria
TAMC	NMT 5 x 10^4 CFU/g or CFU/mL
TYMC	NMT 5 x 10^2 CFU/g or CFU/mL
Bile-tolerant gram-negative bacteria	NMT 1 x 10^2 CFU/g or CFU/mL
Escherichia coli	Absence (1 g or 1 mL)
Salmonella	Absence (25 g or 25 mL)

C. Herbal medicinal products containing, e.g. extracts and/or herbal drugs, with or without excipients, where it can be demonstrated that the method of processing (e.g. extraction with low strength ethanol or water that is not at boiling or low temperature concentration) or, in the case of herbal drugs, of pre-treatment, would not reduce the level of organisms sufficiently to reach the criteria required under B.

Microbiological Quality	**Acceptance Criteria**
TAMC	NMT 5 x 10^5 CFU/g or CFU/mL
TYMC	NMT 5 x 10^4 CFU/g or CFU/mL
Bile-tolerant gram-negative bacteria	NMT 1 x 10^4 CFU/g or CFU/mL
Escherichia coli	Absence (1 g or 1 mL)
Salmonella	Absence (25 g or 25 mL)

D. Special Ph. Eur. provision for oral dosage forms containing raw materials of natural (animal, vegetal or mineral) origin for which antimicrobial pretreatment is not feasible and for which the competent authority accepts TAMC of the raw material exceeding 10^3 CFU/g or CFU/mL.

Microbiological Quality	**Acceptance Criteria**
TAMC	NMT 2 x 10^4 CFU/g or CFU/mL
TYMC	NMT 2 x 10^2 CFU/g or CFU/mL
Bile-tolerant gram-negative bacteria	NMT 1 x 10^2 CFU/g or CFU/mL
Salmonella	Absence (10 g or 10 mL)
Escherichia coli	Absence (1 g or 1 mL)
Staphylococcus aureus	Absence (1 g or 1 mL)

E. Herbal Medicine for External use

Route of Administration	TAMC (CFU/g or CFU/ml)	TYMC (CFU/g or CFU/ml)	Specified microorganisms
Oromucosal use Gingival use Cutaneous use Nasal use Auricular use	NMT 2 x 10^2	NMT 2 x 10^1	Absence of *Staphylococcus aureus* (1 g or 1 ml) Absence of *Pseudomonas aeruginosa* (1 g or 1 ml)
Transdermal patches (limits for one patch including adhesive layer and backing layer)	NMT 2 x 10^2	NMT 2 x 10^1	Absence of *Staphylococcus aureus* (1 patch) Absence of *Pseudomonas aeruginosa* (1 patch)

Notes:
TAMC : Total Aerobic Microbial Count
TYMC : Total Yeasts & Moulds Count
NMT : Not more than
[Reference: latest version of British Pharmacopoeia]

2.7.6 Certificate of Analysis (Active Ingredient)

Applicants shall submit a certificate of analysis for each active ingredient used, which may be purchased from the supplier.

2.7.7 Certificate of Analysis (Finished Product)

The PRH shall submit a Certificate of Analysis (CoA) for the purpose of product registration evaluation. The CoA submitted to NPRA must meet the following requirements:

a) CoA from panel laboratories (certified by NPRA) or local manufacturers' laboratories.
   - Only local laboratories can be accepted as a panel laboratory
   - Refer to NPRA website for the list of panel laboratories
   - Local manufacturers are allowed to issue CoA for their own products only

b) CoA for one (1) batch of local or imported product to be submitted during product evaluation with NPRA's product reference number from QUEST 3+ system.

c) CoA from multiple laboratories for different tests may be accepted, provided that the same batch of the products is submitted to the laboratories.

d) The following compulsory testing parameters shall be stated in the CoA:

Testing parameters	Panel laboratories/ manufacturers' laboratories	Other laboratories
Organoleptic	√	X
Disintegration	√	X
Uniformity of weight	√	X
Microbial Contamination Test	√	X
Heavy Metal Contamination	√	X
Lovastatin (product containing Red Yeast Rice; Monascus purpureus)	√	√
Microcystin (product containing Aphanizomenon flosaquae)	√	√
Assay (for all standardize compounds claimed on label)	√	√

e) For imported products, applicants are required to submit CoA from panel laboratories. Import permit issued by the Centre of Product & Cosmetic Evaluation is required to bring in samples for the purpose of laboratory testing. The applicant should ensure that the import permit is endorsed by the enforcement officer at the entry point.

Reference: Directive No. 8, 2020, BPFK/PPP/07/25 (8) Jld.4. *Direktif Penerimaan Keputusan Pengujian Pra-Pendaftaran Produk Semulajadi dari Makmal Swasta yang Telah Diiktiraf oleh Bahagian Regulatori Farmasi Negara (NPRA) dan Makmal Kawalan Kualiti Pengilang Tempatan* (12 May 2020)

Example of Certificate of Analysis for Finished Product (Natural Product)

Certificate of Analysis

Company name/ Address :

Product Name :

Batch no. :

Dosage form :

Packaging :

Date of manufacture :

Date of expiry :

Test Parameter	Specifications	Results	Method
Appearance/ Organoleptic: Odour Colour	To describe the characteristic		
Disintegration	DRGD		
Uniformity of weight			
Assay: (All standardize compounds claimed on label)	To specify		
Microbial Contamination Test TAMC, TYMC, specified microorganism	DRGD		
Heavy Metal Contamination			
Lead (Pb)	NMT 10 ppm		
Cadmium (Cd)	NMT 0.3 ppm		
Mercury (Hg)	NMT 0.5 ppm		
Arsenic (As)	NMT 5 ppm		

NMT = Not More Than

Signature :
Name :
Designation : (At least by Quality Control Manager or equivalent)
Date of signature :

Note: The above parameter are only as an example, other tests may be required for specific product.

2.8 STABILITY DATA

General:

- The stability of the product is important to ensure the quality of natural product (traditional and homeopathic medicines). This is to ensure that the product specifications are maintained throughout the shelf life of product.

- Effective from 27 Nov 2014, a shelf life of two (2) years shall be approved for both local and imported products. Proposed shelf life exceeding this period will have to be supported by stability study data conducted in Malaysia under Zone IVb conditions (30±2 °C, 75±5%). For further information, refer to circular: *Bil (27).dlm BPFK/PPP/06/04Jld.7 Tempoh Hayat Simpanan* (Shelf-Life) *Bagi Produk Tradisional dan Suplemen Kesihatan* (27 November 2014).

- Should the applicant wish to declare the percentage or content of the isolated compound of a standardized extract, the stability study should state the results of the assay of the isolated compound conducted along the proposed shelf-life. If results of the assay are not provided, the shelf life period approved will not be more than two (2) years.

- The testing frequency of the stability data is as described below:

Storage condition	Testing frequency
Real time	Time 0, 3, 6, 9, 12, 18, 24 months and annually there after through
Accelerated	0, 3 and 6 months

Refer to the ASEAN Guidelines on Stability Study and Shelf Life of Traditional Medicines for further details.

Stability data as shown in the following example shall be submitted for evaluation.

RECOMMENDED PRESENTATION OF THE SUMMARY TABLE OF STABILITY RESULTS

Product Name	:	Storage Temperature, Relative Humidity	:
Dosage Form	:	Batch No.	:
Strength	:	Manufacturing Date	:
Container/Packaging	:	Date of Report	:
Pack Size	:	Period of The Study	:

Testing Parameters (as applicable)	**Specifications**	**Testing Frequency (Months)**							
		0	**3**	**6**	**9**	**12**	**18**	**24**	**36**
Appearance/ Organoleptic characteristics: Odour Colour	To describe the characteristics								
Disintegration	DRGD								
Uniformity of weight	DRGD								
Assay: (All standardized compounds claimed on label, if applicable)	To specify								
Microbial Contamination Test -Total Aerobic Microbial Count -Total Yeasts & Moulds Count -Test for Specified Microorganisms	-NMT 2 x 10^4 CFU/g or CFU/mL -NMT 2 x 10^2 CFU/g or CFU/mL -NMT 1 x 10^2 CFU of bile-tolerant gram-negative bacteria in 1g or 1mL -Absence of Salmonella in 25g or 25mL -Absence of Escherichia coli in 1g or 1mL -Absence of Staphylococcus aureus in 1g or 1mL								
Heavy Metal Contamination -Lead (Pb) -Cadmium (Cd) -Mercury (Hg) -Arsenic (As)	-NMT 10 ppm -NMT 0.3 ppm -NMT 0.5 ppm -NMT 5 ppm		NA						

NMT = Not More Than
Conclusion:

Prepared by: (signature)	Checked by: (signature)	Approved by: (signature)
Name:	Name:	Name:
Designation:	Designation:	Designation:
Date:	Date:	Date:

The tabulated list of parameters for each dosage form is presented as a guide for the following types of tests to be included in a stability study.

Tabulated list of stability indicating parameters for natural products

Testing Parameters / Dosage Form	Organoleptic characteristics	Assay	Hardness/ friability	Dissolution/ Disintegration	Water content	Viscosity	pH	Microbial content	Granules/ Particle Seize variation	Resuspendability	Adhesiveness
Oral powder	√	√			√			√			
Hard capsule	√	√		√	√			√			
Soft capsule	√	√		√				√			
Coated and Uncoated Tablet	√	√	√	√	√			√			
Coated and Uncoated Pill/ Pellet	√	√		√	√			√			
Suspension	√	√				√	√	√	√	√	
Solution	√	√				√	√	√			
Emulsion	√	√				√	√	√			
Semi Solid Preparations (Ointment/ Cream/ Gel/ Lotion/ Paste)	√	√				√	√	√			
Plaster	√	√						√			√
Granules	√	√			√			√	√		
Herbal Infusion Bag/ Herbal Tea Bag	√	√			√			√			
Pastilles	√	√			√			√			

3. PRODUCT SPECIFIC REQUIREMENTS

3.1 FOOT PATCHES

A foot patch that contains herbs with a health claim needs to be registered with the Authority.

Summary of registration for foot patches is described below:

a) Product Indication

- Traditionally used for
  a) General health;
  b) Promoting blood circulation;
  c) Relieve fatigue.

- If there are other indications other than those mentioned above, the applicant is required to submit clinical study data to support the proposed indication.

b) Active ingredient/ Excipient

- The product may only contain active ingredient classified under the category of Natural Products (Traditional).
- Pharmaceutical ingredients with dual function as an active ingredient and excipient, e.g. Vitamin C can be used as excipient.
- However, the maximum allowable amount for the excipient in the traditional product has to follow the pharmacopoeia limits established. If, for example, in the case where the amount of Vitamin C is more than 0.1%, the product shall be classified as an OTC product. The product will then have to fulfill the requirement for the registration of an OTC product.

c) Certificate of Analysis for Finished Product

- It is required with at least one (1) batch data for registration.

d) Certificate of Free Sale (CFS)

- CFS from the regulatory authority of the country of origin of the product depending on the product classification of that product in that country is required.

e) Good Manufacturing Practice (GMP)

- GMP from the governmental issuing body declaring manufacturer adherence to GMP/ ISO or other standards depending on the classification of the product in the country of origin is required.

3.2 HERBAL TEA

Refer to *Bil. (19)dlm.BPFK/PPP/01/03 Jld.3*. *Pekeliling Kriteria Baru Pengkelasan Produk* Food-Drug Interphase (FDI) (7 August 2014)

3.3 HOMEOPATHIC PRODUCTS

Refer to **Appendix 7A: Homeopathic Products**

3.4 NATURAL PRODUCTS WITH THERAPEUTIC CLAIM

Refer to **Appendix 7B: Guideline on Natural Products with Therapeutic Claim**

APPENDIX 7A

HOMEOPATHIC PRODUCTS

The following guidance notes are published as First Edition in October 2010 and the latest revision is in October 2012.

This guidance notes serve as an additional reference on the requirements for the registration of homeopathic products. Other aspects of registration requirements are covered in the Drug Registration Guidance Document. Applicants for product registration are also requested to refer to the latest edition on the Guidelines on Good Manufacturing Practice for Traditional Medicines and Health Supplements.

2nd Revision
Acknowledgements

The National Pharmaceutical Regulatory Agency acknowledges its indebtedness to the Malaysia Homeopathic Medical Council and the Traditional & Complementary Medicine Division, Ministry of Health who provided comments and advice during the preparation of these guidelines.

Glossary for Homeopathic Products:

Active substance: Active substances are considered to be source materials processed by one or a sequence of homeopathic manufacturing procedures listed in pharmacopoeias in official use and other officially recognized documents (e.g. mother tinctures, dilutions or triturations).

Diluent: Substance used for the preparation of a stock/ starting material or the potentisation process and which may also represent the substance of the dosage form. Liquid diluents usually consist of purified water, aqueous solution, glycerol or ethanol of a suitable concentration or for which there is an appropriate monograph. The commonest solid diluent is usually lactose monohydrate.

Dilution: Dilution has two meanings in homeopathy:

- For a product, a dilution is a liquid homeopathic preparation which is potentised as described below (see the definition of potentisation). Individual dilutions are also called potencies;
- As a procedure, dilution means the de-concentration process of a liquid or a solid preparation. One part of each stage in the preparation of a homeopathic medicine from its stock or previous dilution (potency) by adding one part of a previous solid or liquid phase to a predetermined weight or volume of the diluent (see Potentisation below). Dilution occurs at all stages of production of the homeopathic medicines whether by addition of solid excipient in trituration or the addition of diluent in the liquid phase and succussion.

Dosage form: a dosage form in homeopathy complies with any relevant specifications for that dosage form for which an appropriate characterization exists in a pharmacopoeia in official use, or in other officially recognized documents. The most commonly encountered homeopathic dosage form, *the globule (pillule or pellet)*, is a solid spherule which consists of lactose, sucrose or any other suitable vehicle. Usually, preformed globules are impregnated with a dilution or directly by a mother tincture. The homeopathic dosage form *tablet* is a solid preparation which complies with any relevant characterization in the pharmacopoeia in official use (or in other officially recognized documents) for tablets. Homeopathic medicines in tablet form are either prepared by impregnation of preformed tablets or by compression of triturations with the vehicle. The most commonly used *liquid homeopathic medicines* are either alcoholic solutions or oral liquids.

Excipient: Substance needed for manufacturing a dosage form (used after potentisation) such as wheat starch and magnesium stearate for tablets. It may also represent the substance of the dosage form.

Homeopath: A qualified provider (practitioner) of homeopathic treatment.

Homeopathic medicines: Any medicine prepared in accordance with a homeopathic manufacturing procedure described by a pharmacopoeia in official use or other officially recognized documents. A homeopathic medicine may contain a number of homeopathic preparations.

Homeopathy: Classical homeopathy is a system of medicine using preparations of substances whose effects, when administered to healthy subjects, correspond to the manifestations of the disorder in the individual patients.

Mother tincture (also called tincture): The initial homeopathic preparation made from source material that can be further potentised (also called "liquid stock"), sometimes used as homeopathic medicines, is regarded as the most concentrated form of a finished homeopathic medicine. Mother tinctures are obtained classically by maceration or percolation (sometimes also by digestion, infusion, decoction or fermentation) techniques from source materials according to a procedure prescribed by a recognized homeopathic pharmacopoeia. Sometimes a mother tincture corresponds to the first decimal dilution, "1D" or "1X" (10-1), mostly when dry plant material is used as starting material.

Nosodes: Homeopathic medicines prepared from disease products from humans or animals; from pathogenic organisms or their metabolic products; or from decomposition products of animal organs.

Potency: The denominated degree of serial trituration or dilution and succession that is reached for each homeopathic medicine. The degrees of dilution or potencies are normally indicated by the letters D, DH or X for successive 1 to 10 (decimal) dilutions, the letters C, CH or K or CK for successive 1 to 100 (centesimal) dilutions while Q or LM denote successive 1 to 50 000 (Hahnemannian quinquagintamillesimal) dilutions. Dilution by 1 to 10 denotes 1 part processed with 9 parts of diluent (Hahnemannian decimal), dilution by 1 to 100, 1 part processed with 99 parts (Hahnemannian or Korsakovian centesimal), and so on. The number preceding the letters (e.g. D, C or LM) normally indicates the number of dilution steps employed (Table 1).

As a consequence of different views in various approaches in homeotherapy and because the notion of these terms may depend on the nature of the starting materials, the terms "high potency" and "low potency" cannot be defined unambiguously.

Potentisation (also called dinamization)**:** The combined process of serial dilution and succussion or trituration at each step in the manufacture of homeopathic medicines from stocks. (According to the tenet of homeopathy, potentisation represents the process by which the activity of a homeopathic medicine is developed.)

Table I: Potency table

Dilution ratio	Common designation(s)	Examples
1:10[a]	X	1X, 2X, 3X, etc.
1:10[a]	D	D1, D2, D3, etc.
1:10[a]	DH	DH1, DH2, DH3, etc.
1:100[b]	C	1C, 2C, 3C, etc. C1, C2, C3, etc.
1:100[b]	CH	1CH, 2CH, 3CH, etc. CH1, CH2, CH3, etc.
1:100[b]	CK	1CK, 2CK, 3CK, etc. CK1, CK2, CK3, etc.
1:100[b]	K	1K, 2K, 3K, etc. K1, K2, K3, etc.
1:50 000[a]	LM	1LM, 2LM, 3LM, etc.
1:50 000[a]	Q	Q1, Q2, Q3, etc.

[a]For 1:10 and 1:50 000 dilution ratios only the Hahnemannian method of manufacture (multi-flask method) is used.

[b]For 1:100 dilution ratios a C potency is assumed to use the Hahnemannian method of manufacture (multi-flask method) and can also be denoted as CH. When the Korsakovian method of manufacture (single-flask method) is used, the potency is designated as CK or K.

Sarcodes: Homeopathic medicines made from healthy animal tissues or secretions. In Greek, sarcode means fleshly.

Source material (raw material, starting material, mother substance): Source material is the original raw material used for the production of homeopathic medicines. This material is obtained from natural sources, e.g. of botanical, zoological, microbiological, mineral, chemical, animal and human origin, or synthetic procedures. Source materials may undergo preliminary treatment in order to be further processed.

Stock: Substances or preparations made from the source materials (e.g. by maceration, succussion or trituration) used as starting points for the production of homeopathic medicines.

Outline:

1. Introduction
2. Exemptions
3. Preparations not considered by the Authority for registration
4. Ingredients
5. Quality
6. Good Manufacturing Practice
7. Labelling
8. Indications for use

Attachments:

- Attachment 1: List of Exempted Single Homeopathic Potentised Dilutions
- Attachment 2: Negative List
- Attachment 3: List of Acceptable References
- Attachment 4: List of Endangered Animal Species/ Protected Wildlife

1. INTRODUCTION

Regulation 7(1)(a) of the Control of Drugs and Cosmetics Regulations (CDCR) 1984 requires all products to be registered with the Authority prior to being manufactured, sold, supplied, imported or possessed for sale, unless the product is exempted under the specific provisions of the regulations.

Under Regulation 2, CDCR 1984, "**Homeopathic medicine**" means any pharmaceutical dosage form used in the homeopathic therapeutic in which diseases are treated by the use of minute amounts of such substances which are capable of producing in healthy persons symptoms similar to those of the disease being treated. This would include preparations that are to be chewed, sucked, swallowed whole and applied topically.

Applicants are reminded that it is their responsibility to ensure that their products comply with these regulations and also other related legislations namely:

(i) Sale of Drugs Act 1952

(ii) Dangerous Drugs Act 1952

(iii) Poisons Act 1952

(iv) Medicines (Advertisement & Sale) Act 1956

(v) Protection of Wildlife Act, 1972

2. EXEMPTION

All homeopathic products are registrable under the *Control of Drugs and Cosmetics Regulations 1984*. Exemption to this are:

i) single homeopathic potentised dilution;

ii) extemporaneous preparation for an individual patient by a registered/ licensed homeopathic practitioner;

iii) All Mother Tinctures;

iv) Unmedicated sugar globules and tablets.

3. PREPARATION NOT CONSIDERED BY THE AUTHORITY FOR REGISTRATION

The Authority will only register homeopathic products used for oral administration, nasal or mouth sprays and external application only. The following dosage forms will not be considered for registration.

- Sterile preparations such as eye-drops and injectables;
- Suppositories and vaginal tablets;
- Transdermal patch;
- Sublingual preparations;
- Preparation in combination with non-homeopathic active ingredient, such as vitamins, minerals and herbs.
- Preparations containing substance listed in the Poison List (except **Attachment 1**).

4. INGREDIENTS

Homeopathic products are prepared from natural or synthetic sources that are referenced in pharmacopoeia monographs or other recognized documents. Not considering imponderable, the source materials for homeopathic medicines may consist of the following:

- Plant material such as: roots, stems, leaves, flowers, bark, pollen, lichen, moss, ferns and algae;
- Microorganisms such as: fungi, and plant parasites;
- Animal materials such as: whole animals, animal organs, tissues, secretions;
- Minerals and chemicals.

For each medicinal ingredient, a copy of the monograph from the pharmacopoeia to which the applicant attests must be provided. Also for homeopathic medicines with a specific claim, it must be supported by the same level of evidence as for traditional products.

Products containing a combination of homeopathic and non-homeopathic medicinal ingredient will not be evaluated as a homeopathic product.

4.1 POSITIVE LIST

Homeopathic medicinal ingredients are allowed as multi ingredient in homeopathic products and the active ingredient must be documented in a monograph as a homeopathic medicinal ingredient as stated in the current edition of Homeopathic Pharmacopoeias recognized by the Authority listed in **Attachment 3**.

Homeopathic products are allowed to be registered when the homeopathic medicinal ingredients used in their products are more than 2C or 4X.

4.2 NEGATIVE LIST

Homeopathic products containing single or multiple ingredients in **Attachment 2** and **Attachment 4** will not be registered by the Authority.

4.3 LIMIT OF HOMEOPATHIC INGREDIENTS IN MULTI INGREDIENT HOMEOPATHIC PRODUCTS

Homeopathic Products are allowed to contain a maximum of 12 potentised single homeopathic dilutions.

5. QUALITY

A certificate of analysis (CoA) for raw material potentised dilution and finished product must be provided as proof on the dilution used.

6. GOOD MANUFACTURING PRACTICE

The requirements for Good Manufacturing Practice of the premises as outlined in the Guidelines on Good Manufacturing Practice for Traditional Medicines and Health Supplements apply to all homeopathic products.

7. LABELLING

The labelling of homeopathic products is the same as for traditional products in DRGD with the following additional requirements:

On the label of this homeopathic product:

a) The word 'homeopathic product', 'homeopathic medicine', 'homeopathic preparation', 'homeopathic remedy' (either one) - must appear on the innermost label of the container.
b) The scientific name or common name of the active ingredient.
c) Potency and type of scale use.
d) Declare the percentage of alcohol contained in the product.

8. INDICATIONS FOR USE

Indications allowed for homeopathic product is the same as those allowed for traditional products in the DRGD.

Recommended use or indications for specific claims must be supported by evidence for the multi ingredient homeopathic products.

No indication will be allowed for single homeopathic potentised dilution in the form of raw material and finished homeopathic product. No indications are also allowed for mother tinctures.

ATTACHMENTS

Attachment 1:

List of "Single Homeopathic Potentised Dilution (2C or 4X or 1:10000)" exempted from the Poisons List.

No.	Ingredient
1.	Aconite
2.	Amyl nitrite
3.	Antimony
4.	Apomorphine
5.	Arsenic
6.	Barium
7.	Belladonna
8.	Bismuth
9.	Boric Acid
10.	Caffeine
11.	Cantharidin
12.	Colchinine
13.	Coniine
14.	Creosote
15.	Curare
16.	Digitalis
17.	Ephedra
18.	Ergot
19.	Gelsemium
20.	Hydrogen Cyanide
21.	Hyoscine
22.	Iodine
23.	Jaborandi
24.	Lead Acetate
25.	Lobelia Inflata
26.	Mercury

No.	Ingredient
27.	Morphine
28.	Nicotine
29.	Nux Vomica
30.	Phosphorus
31.	Physostigmine
32.	Picric Acid
33.	Piper Methysticum (Kava-kava)
34.	Quebracho
35.	Quinine
36.	Radium
37.	Rauwolfia
38.	Sabadilla
39.	Santonin
40.	Sparteine
41.	Stavesacre
42.	Strophanthus
43.	Thallium
44.	Veratrum
45.	Vinca
46.	Yohimba

Attachment 2:

Negative List

NO.	SUBSTANCES
1.	**Mother tincture of Narcotics**
	Homeopathic Products
	Cannabis
	Cocainum
	Cocainum muriaticum
	Coca leaves
	Narceinum
	Opium
2.	**Mother tincture of Radiopharmaceuticals**
	Uranium
	X-ray
3.	**Mother tincture of Animal materials: Nosodes, toxins and blood products**
4.	**Mother tincture of human or human organ**
5.	**Mother tincture of Bacteria**
6.	**Mother tincture of Viruses**

Attachment 3:

Homeopathic Pharmacopoeia from the Following Countries Will Be Accepted as References

NO.	COUNTRIES
1.	Germany (GHP)
2.	Britain
3.	France (Phf)
4.	USA (HPUS)
5.	Pakistan
6.	India (HPI)
7.	European Pharmacopoeia

Attachment 4:

List of Endangered Animal Species/ Protected Wildlife

As listed in the Protection of Wildlife Act, 1972

Notes:
These lists are not exhaustive and will be amended from time to time as and when the need arises

REFERENCES

a) List of Ingredients Prohibited and Restricted in Pregnancy

1. Benchmarks for training in traditional Chinese medicine (WHO)
2. American Pregnancy Association
3. Natural Standards
4. Health Canada
5. TCM Discovery (Contraindication of Chinese Medicinal Herbs)
6. Motherlove Herbal Company (Herbs to avoid while Pregnant)
7. Green Earth Herbs (Herbs Contraindicated in Pregnancy)
8. Home. Caregroup.Org (Herbs during Pregnancy and Lactation)

b) Homeopathic Products:

1. Safety Issues in the Preparation of Homeopathic Medicines, World Health Organization, 2009.

APPENDIX 7B

GUIDELINE ON NATURAL PRODUCTS WITH THERAPEUTIC CLAIM

Guidance documents are meant to provide assistance to industry and healthcare professionals on how to comply with governing statutes and regulations. They also serve to provide guidance to National Pharmaceutical Regulatory Agency (NPRA) officers, thereby ensuring transparency, fairness, and consistency in assessment of quality, safety and efficacy of a product.

Guidance documents are tools to assist stakeholders and do not have the force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document will be acceptable if they support an equivalent outcome resulting in high quality of natural products.

This document should be read in conjunction with the current laws and regulations, and with other relevant legislation as outlined in the current guidance document (Drug Registration Guidance Document, DRGD), which include ASEAN Common Technical Dossier/ Requirements (ACTD/ ACTR), Malaysian Guideline for Application of Clinical Trial Import Licence and Clinical Trial Exemption, Malaysian Guideline for Good Clinical Practice (GCP), Pharmaceutical Inspection Co-Operation Scheme (PIC/S) Guide to Good Manufacturing Practice for Medicinal Products, as well as relevant sections of any other applicable guidance documents.

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1.0 INTRODUCTION

Natural products with therapeutic claims are required to be registered with the Drug Control Authority (DCA) before they can be marketed in Malaysia. This guideline aims to provide the requirements to support the quality, safety and efficacy of the natural product with therapeutic claims.

All therapeutic claims made for natural products should have adequate evidence to support all indications, and all claims made must be demonstrated to be true, valid and not misleading. The quality, safety and efficacy of the product should be proven, and the relevant data should be submitted to the DCA.

This guideline aims to provide guidance on making unbiased and truthful claims, supported by adequate evidence in order to protect the consumers from misleading claims.

2.0 SCOPE OF THIS GUIDELINE

This guideline encompasses the type of evidence to support the therapeutic claim for a natural product intended for human use. It also outlines what are the quality and safety data required and applicable to products containing herbal/ plant–medicinal ingredients in the form of standardized extract. The natural product with therapeutic claims shall not include any sterile preparation, any vaccines, any substance derived from human parts, any isolated and characterized chemical substances.

3.0 DEFINITION

3.1 THERAPEUTIC CLAIM:

A claim that is not documented in established pharmacopoeia or monographs, or a claim which is not the traditional use of the ingredient. It may include corroboration and verification of traditional use to relieve a symptom or help to treat a disease, disorder or medical condition, and it must be substantiated by scientific evidence.

The efficacy of a product and its ingredient(s) shall be based on the totality of the substantiation evidence provided including human study, non-clinical and empirical or historical data, as well as other documented evidence, where applicable on the end product. The study must show a consistent association between the active ingredient/herbal ingredient(s) and the therapeutic effect claimed.

The products with therapeutic claims must be manufactured in a Good Manufacturing Practice (GMP) compliant premises which follows the Pharmaceutical Inspection Co-Operation Scheme-Guide to Good Manufacturing Practice for Medicinal Products (PIC/S) guideline.

Non-clinical safety studies for therapeutic claims must be conducted in a facility which complies to Organisation for Economic Cooperation and Development (OECD) Good Laboratory Practice (GLP) requirement as mentioned in Directive No. 9, 2016, *Bil. (40) dlm.BPFK/PPP/07/25 Keperluan* Good Laboratory Practice (GLP) *bagi Kajian Keselamatan Bukan Klinikal Untuk Tujuan Pendaftaran Produk* New Chemical Entity (NCE)*, Biologik dan Produk Herba Dengan Tuntutan Terapeutik Tinggi.*

The Authority may request for further information or specify conditions not described in this document that is deemed necessary to ensure the quality, safety and efficacy of the product.

4.0 REGULATORY/ REGISTRATION REQUIREMENTS

The requirements for registration shall be in accordance with the **ASEAN Common Technical Dossier (ACTD)** format and in adherence to the general regulatory requirement as described in sections of the main Drug Registration Guidance Documents (DRGD), **Appendix 15, 1.1 General Requirements For Full Evaluation**. It covers:

- Part I - Administrative data and product information
- Part II - Data to support product quality (Quality Document)
- Part III - Data to support product safety (Nonclinical Document)
- Part IV - Data to support product safety and efficacy (Clinical Document)

4.1 ADMINISTRATIVE DATA AND PRODUCT INFORMATION (PART I)

Primary purpose: To provide a general introduction to the product. The Administrative Data is where required specific documentation in detail is put together such as application forms, label, package insert etc. Product Information contains necessary information which includes prescribed information, mode of action, side effects etc.

4.2 QUALITY DOCUMENTS (PART II)

Primary purpose: The product and its ingredient(s) is determined by the quality of the starting material, development, in-process controls and process validation, and by specifications applied to them throughout development and manufacture.

4.2.1 Authentication of the medicinal plants/ ingredients

4.2.1.1 Collection/ cultivation and/or harvesting of medicinal plants/ ingredients should follow other relevant guidance such as the Malaysian Standard on Good Agricultural Practice (GAP) – Part 8: Herbs (MS: 1784-8:2009)

4.2.1.2 The botanical identity such as the scientific name (genus, species, sub-species/ variety, author and family) - of each medicinal plant should be verified by qualified experts from government agencies or other qualified agencies.

4.2.1.3 The authentication of the medicinal plant/ ingredient must be determined following the parameters in established monographs/ pharmacopeias.

4.2.1.4 The botanical source, plant part used and its state (e.g.: whole, reduced, powdered, fresh, dry) should be defined.

4.2.1.5 Requested tests are listed as below, while specifications should be supported by established monographs/ pharmacopeia:

Tests	Specifications	Results
Appearance/Organoleptic characteristics		
Qualitative Test: Identification/ Macroscopic/Microscopic/ Chemical fingerprint		
Loss on drying / Water content		
Purity tests • Foreign Matter • Total Ash Content • Acid insoluble ash*		
Extractive values* • Water Soluble • Ethanol Soluble		
Microbial Contamination Test: - • Total Aerobic Microbial Count (TAMC) • Total Yeast and Mold Count (TYMC) • Bile tolerant gram-negative bacteria		

Tests	Specifications	Results
• *Salmonella* • *Escherichia coli* • *Staphylococcus aureus* • *Pseudomonas aeruginosa*		
Heavy metal limits: - • Arsenic • Mercury • Lead • Cadmium		
Other Tests (any required testing)		

** These tests might not apply to all medicinal plant/ingredient and must be justified by the applicant.*

4.2.2 Information on the standardized extracts

4.2.2.1 To state the botanical source and type of preparation (e.g.: dry or liquid extract). Ratio of herbal substance to the genuine herbal preparation must be stated.

4.2.2.2 Information on the standardized extracts used in products shall be provided which include (but not limited to);

(i) chemical marker/ biomarker of the standardized extracts
(ii) information on the solvent system used to obtain the standardized extracts
(iii) method of identification of Active Ingredient(s) in the standardized extracts
(iv) method of quantification of Active Ingredients(s) in the standardized extracts

4.2.2.3 Methods used for both identification and quantitative analysis need to be validated

4.2.2.4 Applicants shall refer to Checklist for Protocol Analysis and Analytical Method Validation available in NPRA website for details of the test methods.

4.2.2.5 Quality Control of the Standardized Extracts

(i) Protocol of Analysis for the tests on standardized extracts must be provided.
(ii) Requested tests are listed as below, while specifications should be supported by established monographs/ pharmacopeia:

Tests	Specifications	Results
Appearance/ Organoleptic characteristics		
Qualitative Test: Identification		
Quantitative Assay		
Loss on drying / Water content		
Microbial Contamination Test: - • Total Aerobic Microbial Count (TAMC) • Total Yeast and Mould Count (TYMC) • Bile tolerant gram-negative bacteria • *Salmonella* • *Escherichia coli* • *Staphylococcus aureus* • *Pseudomonas aeruginosa*		
Heavy metal limits: - • Arsenic • Mercury • Lead • Cadmium		
Impurities • Related/ degraded substance • Pesticide residues • Solvent residues		
Adventitious Toxins • Aflatoxins		
Other Tests (any required testing)		

(iii) Certificate of Analysis (CoA) for the standardized extracts need to be attached (**minimum of 2 batches**).

4.2.3 Finished Product Formulation

4.2.3.1 Description/ Physical characteristics/ Appearance/ Organoleptic characteristic

4.2.3.2 Information on the complete formulation of the product which include:

(i) Scientific name of the ingredient and the part used
(ii) Name of active ingredient(s)/ Standardized extract(s)
(iii) Name of other ingredients(s) e.g. adjuncts, excipients, preservative, colour, flavours
(iv) Strength of each ingredient

4.2.3.3 Standardization of Extract

For example: The extract is standardized to contain:
-X% of compound A (assayed by HPLC/UV etc)
-Y% of compound B (assayed by HPLC/UV etc)

4.2.3.4 Quality Control of Finished Product

(i) Protocol of Analysis for the tests on finished product must be provided.
(ii) Methods used for both identification and quantitative analysis need to be validated
(iii) Tests and Specification Limits (Shelf-life and Release Specifications)

Tests	Specifications	Results
Appearance/Description of the dosage form		
Identification		
Quantitative Assay		
Microbial Contamination Test: - • Total Aerobic Microbial Count (TAMC) • Total Yeast and Mould Count (TYMC) • Bile tolerant gram-negative bacteria • *Salmonella* • *Escherichia coli* • *Staphylococcus aureus* • *Pseudomonas aeruginosa*		
Heavy metal limits: - • Arsenic • Mercury • Lead • Cadmium		
Uniformity of weight (for tablets & capsules)		
Disintegration (for pills, tablets & capsules)		

Tests	Specifications	Results
Impurities • Related / degraded substance • Pesticide residues • Solvent residues		
Adventitious Toxins • Aflatoxins		
Other Tests (any required testing)		

(iv) Certificate of Analysis (CoA) for the finished products need to be attached (**minimum of 2 batches**).

4.2.3.5 Validation of Analytical Method (Microbial Contamination Test, Heavy Metal Test and Quantitative Assay of the Finished Product)

Validation Reports must be submitted and their contents should include:

(i) Introduction
(ii) Specificity
(iii) Repeatability
(iv) Linearity
(v) Range
(vi) Accuracy
(vii) Precision
(viii) Precision (intermediate precision/ruggedness)
(ix) System suitability testing
(x) Detection Limit (if applicable)
(xi) Quantitation Limit (if applicable)
(xii) Conclusions

Applicant shall refer to Checklist for Protocol Analysis and Analytical Method Validation available in NPRA website for details of the data to be submitted.

4.2.3.6 Information on the laboratory/ies

If quality control tests are conducted by an external laboratory, the following information should be stated:

(i) Name and address of the laboratory
(ii) Type of tests conducted by the external laboratory
(iii) Reasons why the tests are not performed by the manufacturer

4.2.4 Stability of Product

a) Storage condition to be included on the label.

b) Proposed shelf life.
- Stability studies/ completed stability studies/ accelerated stability studies should include summary of stability studies, characteristic and degradation products monitored, results and conclusions of completed stability studies.
- Stability studies results/data for 2 batches are required.

c) Outline of on-going or proposed stability studies
- Stability studies must be carried out in accordance to ASEAN/ ICH Stability Studies Guidelines.

4.2.5 Containers/ Packaging

a) Immediate containers/ packaging
- Type
- Material
- Capacity, where applicable
- Closure and liner (type and material), where applicable

b) Other container(s)/ packaging(s)

c) Dose-measuring device/ applicators/ administration set/ etc. if any
- Description/ Type
- Material
- Capacity, where applicable

d) Packaging inclusions (desiccant, filler, etc.) if any
- Description and compositions

e) Any known interaction between the product and packaging material, if any.

4.3 NON-CLINICAL DOCUMENT (PART III)

Primary purpose: To provide a comprehensive, factual synopsis of the non-clinical data. The non-clinical studies should be conducted prior to the initiation of any clinical studies. Therefore, the interpretation of the data, the clinical relevance of the findings, cross-linking with the quality aspects of the pharmaceutical, and the implications of the nonclinical findings for the safe use of the natural product should be addressed in the nonclinical overview.

In vitro studies as well as animal studies (*in vivo*) are intended to generate the non-clinical data. Data from animal study should be derived from animal model which can represent human condition related to claim. The methodology should be an acceptable and valid procedure to measure the parameter. Data from animal studies are important to give the preliminary efficacy and safety data prior to the conduct of human study. When data from animal (*in vivo*) and *in vitro* studies are submitted as substantiation of claims, an explanation on its relevance to humans should be included.

Requirements:

4.3.1 Should present an integrated and critical assessment of the pharmacologic, pharmacokinetic and toxicologic evaluation.

4.3.2 Relevant scientific literature of related active ingredient(s) of product can be considered as an additional supporting document.

4.3.3 Non-clinical studies must be conducted in OECD GLP compliance facility.

4.3.4 Content and Structural Format:
4.3.4.1 Overview of the Nonclinical Testing Strategy
4.3.4.2 Pharmacology
4.3.4.3 Pharmacokinetics
4.3.4.4 Toxicology
4.3.4.5 Integrated Overviews

4.3.5 Nonclinical Written Summaries Format:
4.3.5.1 Introduction
4.3.5.2 Pharmacology written summary
4.3.5.3 Pharmacology tabulated summary
4.3.5.4 Pharmacokinetics written summary
4.3.5.5 Pharmacokinetics tabulated summary
4.3.5.6 Toxicology written summary
4.3.5.7 Toxicology tabulated summary

4.4 CLINICAL DOCUMENT (PART IV)

Primary purpose: The clinical section addresses the requirements for pharmacokinetic, pharmacodynamic, efficacy and safety studies.

Scientific data should be derived from intervention human studies, that are well designed in accordance with recognized scientific principles, with statistically and clinically significant outcomes addressing the specific traditional claim. The acceptable principles for human studies can be referred to internationally accepted guidelines, for example, ICH-GCP Guidelines.

Requirements:

4.4.1 Should describe and explain the overall approach to the clinical development of a product.

4.4.2 Assess the quality of the design and performance of the studies, and to include a statement regarding GCP compliance.

4.4.3 Scientific evidence from human studies on end-product.

4.4.4 Content and Structural Format of Clinical Overview:
4.4.4.1 Product Development Rationale
4.4.4.2 Overview of Natural Product Formulations
4.4.4.3 Overview of Clinical Pharmacology
4.4.4.4 Overview of Efficacy/Claim benefits
4.4.4.5 Overview of Safety
4.4.4.6 Benefits and Risks Conclusions

4.4.5 Clinical Written Summaries Format:
4.4.5.1 Product Development Rationale
4.4.5.2 Overview of Natural Product Formulations
4.4.5.3 Overview of Clinical Pharmacology
4.4.5.4 Overview of Efficacy
4.4.5.5 Overview of Safety
4.4.5.6 Benefits and Risks Conclusions

4.4.6 Relevant scientific literature of related active ingredient(s) of product can be considered as an additional supporting document. Any deviation should be discussed and justified.

Examples of scientific evidence:

- Evidence obtained from at least one properly designed randomized controlled (preferably multi-centre) double blind trial. It is preferable to have data from at least two trials independent of each other, but in some cases, one large well-conducted trial may suffice.

- Evidence can be obtained from well-designed controlled trials with or without randomization.
- Systematic reviews of the clinical research relating to particular subject areas
- Peer reviewed scientific data or meta-analysis (these evidences must be product specific and published in reputable peer reviewed journals)

Where there are differences between the ingredient and reported therapeutic benefit, a justification will be required in your evidence package to address the discrepancy.

Non-clinical studies, cellular or pharmacological studies, these alone are not considered sufficient evidence to support a scientific indication. However, such studies can be used to provide secondary support to human data.

Internationally recognised monographs and pharmacopoeias can also provide additional support to specific indications referring to health enhancement claims, but such items will need further evidentiary support from primary research articles and/or systematic reviews. The more specific the indication, the more evidence you need to provide to support your indication.

5.0 GLOSSARY

Active ingredient - The therapeutically active component in a medicine's final formulation that is responsible for its physiological action

Clinical Trial/ Study - Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s) and/or to identify any adverse reactions to an investigational product(s) and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

Efficacy – a relative concept referring to the ability of a medicine or treatment to achieve a beneficial clinical effect. This may be measured or evaluated using objective or subjective parameters.

Product - a drug in a dosage unit or otherwise, for use wholly or mainly by being administered to one or more human beings or animals for a medicinal purpose; or a drug to be used as an ingredient of a preparation for a medicinal purpose.

Scientific evidence – a quantifiable data and usually includes reports of clinical trials in humans, human epidemiological studies, animal studies and other cellular or pharmacological studies. Due to the quantifiable nature of scientific evidence, scientific indications can imply clinical efficacy where the indication is supported by such data.

6.0 REFERENCES

1. Final concept paper on the implementation of different levels of scientific evidence in core-data for herbal drugs. EMEA/CPMP/ HMPWP/1156/03
2. Guidelines on the evidence required to support indications for listed complementary medicines, Therapeutic Good Administration (TGA), Version 3.0, January 2019.
3. General guidelines for methodologies on research and evaluation of traditional medicine, WHO/EDM/TRM/2000.1
4. Malaysian Guideline for Application of Clinical Trial Import Licence and Clinical Trial Exemption (Appendix D5: Pharmaceutical Data Format for Herbal/ Natural Products in Clinical Trials),
5. Drug Registration Guidance Document (DRGD) – available at website *www.npra.gov.my*
6. ASEAN Common Technical Dossier/ Requirements (ACTD/ ACTR)
7. Malaysian Standard Guideline on Good Agricultural Practice (GAP) – Part 8: Herbs MS: 1784-8:2009
8. Annex VII ASEAN guidelines on claims and claims substantiation for traditional medicines (Version 2.0)
9. Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products. EMA/HMPC/162241/2005 Rev. 2

APPENDIX 8

SUPPLEMENTARY DOCUMENTATION

(PARTICULARS OF PRODUCT OWNER AND MANUFACTURER)

Product Owner

Please select one of the following for status of product owner:

- Manufacturer or
- Product registration holder or
- Product registration holder & manufacturer or
- Others (If the product owner is neither of the above status) – Please enter name and address of the product owner.

Letter of Authorization from Product Owner

- All applications for registration shall be accompanied with Letter of Authorization from product owner.
  (Not applicable if the Product Registration Holder is Product Owner).

- Letters of Authorization (LOA) shall be valid and current at the time of submission.

- The LOA shall be on the product owner's original letterhead and be dated and signed by the Managing Director, President, CEO or an equivalent person who has overall responsibility for the company or organization.

- The LOA shall state the name of the product concerned and also the name and actual plant address of the manufacturer(s) involved in the manufacture of the product.

Letter of Appointment of Contract Manufacturer from Product Owner

- Please attach (if applicable).

- Applicable for product which is contract manufactured by a manufacturer who is not the product owner.

Letter of Acceptance from Contract Manufacturer

- Please attach (if applicable).

- The letter of acceptance from the manufacturer shall be on the manufacturer's original letterhead and be dated and signed by the Managing Director, President, CEO or an equivalent person who has overall responsibility for the company or organization.

- The letter of acceptance shall state the name of the product concerned and also the name and actual plant address of the manufacturer(s) involved in the manufacture of the product.

APPENDIX 9

FEES

Outline:

1. Charges for USB Token of QUEST Membership;
2. Processing and Analysis Fees for Product Registration;
3. Charges for Application of Licenses;
4. Charges for Amendments to Particulars of a Registered Product;
5. Fees for Certificates; and
6. Charges for Product Classification.

1. CHARGES FOR USB TOKEN OF QUEST MEMBERSHIP

No.	Type	Validity Period	
		1 year (RM)	2 years (RM)
1.	Main User – New, Replacement, Change of Authorized Person (Certificate + USB Token)	260	290
2.	Supplementary User – New, Replacement, Change of Authorized Person (Certificate + USB Token)	245	275
3.	Change Authorized Person (Certificate Only)	48	95
4.	Renewal (Digital Certificate only – using existing MSC USB Token)	48	95
5.	Postage (*Semenanjung* Malaysia)	10	
6.	Postage (Sabah/ Sarawak)	20	

2. PROCESSING AND ANALYSIS FEES FOR PRODUCT REGISTRATION

Every application for registration shall be submitted with the appropriate processing and analysis fees, as specified below (effective 1 January 2007):

No.	Category of Product	* Processing Fees (RM)	Analysis Fees (RM)	Total Fees (RM)
1.	Pharmaceutical a) New Drug Products b) Biologics	1,000.00	Single active ingredient: 3,000.00	4,000.00
			Two or more active ingredients: 4,000.00	5,000.00
2.	Pharmaceutical a) Generic (Scheduled Poison) b) Generic (Non-Scheduled Poison) c) Health supplement	1,000.00	Single active ingredient: 1,200.00	2,200.00
			Two or more active ingredients: 2,000.00	3,000.00
3.	Natural Product	500.00	700.00	1,200.00
4.	Natural products with therapeutic claim	1,000.00	Single active ingredient: 3,000.00	4,000.00
			Two or more active ingredients: 4,000.00	5,000.00

** As stipulated under Regulation 8, CDCR 1984,*

3. CHARGES FOR APPLICATION OF LICENSES

After a product is registered, the applicant shall apply for a manufacturer's/ import/ wholesaler's license.

The processing fees are as specified below:

License	Processing Fees (RM)	Timeline	Validity
1. Manufacturer's	1,000.00	4 working days upon receipt of complete application	1 year
2. Import	500.00	4 working days upon receipt of complete application	1 year
3. Wholesaler's	500.00	4 working days upon receipt of complete application	1 year

4. CHARGES FOR AMENDMENTS TO PARTICULARS OF A REGISTERED PRODUCT

4.1 CHANGE OF MANUFACTURING SITE & CHANGE OF PRODUCT REGISTRATION HOLDER

Types of Amendment	Processing Fees	
	Pharmaceutical (RM)	Natural Product (RM)
1. Change of Manufacturing Site (Type I)	1,000.00	100.00
2. Change of Manufacturing Site (Type II, III, IV, V)	1,000.00	500.00
3. Change of Product Registration Holder	1,000.00	500.00

4.2 VARIATION & ADDITIONAL INDICATION

Types of Amendment	Processing Fees	
	Full Evaluation (RM)	Abridged Evaluation (RM)
1. Minor Variation Prior Approval (MiV-PA)	150.00	50.00
2. Major Variation (MaV)	300.00	100.00
3. Additional Indication	1000.00	Not applicable

5. FEES FOR CERTIFICATES

Under Regulation 16, CDCR 1984:

"The Director of Pharmaceutical Services may issue such certification on any matter relating to any product where such certification is required by any country importing such a product."

Certificates	Fees (RM)	Validity
Issuance of one (1) Certificate of Pharmaceutical Product	50.00	2 years
Issuance of one (1) Certificate of Good Manufacturing Practice (GMP)	50.00	2 years
Issuance of one (1) Certificate of Declaration (*Sijil Deklarasi*)	50.00	-
Issuance of one (1) Certificate of Indication (*Sijil Indikasi*)	50.00	-

6. CHARGES FOR PRODUCT CLASSIFICATION

Processing Fees	Timeline
RM300 per product for each application	14 working days upon receipt of complete and satisfactory application

APPENDIX 10

DATA EXCLUSIVITY

1. INTRODUCTION

Data exclusivity refers to protection of undisclosed, unpublished and non-public domain pharmaceutical test data, the origination of which involves considerable effort, submitted as required to the Director of Pharmaceutical Services for the purpose of scientific assessment in consideration of the:

a) Quality, safety and efficacy of any new drug product containing a New Chemical Entity

b) Safety and efficacy for a second indication of a registered drug product as a condition for registration of any new drug product containing a New Chemical Entity; or approval for a Second Indication of a registered drug product.

For information on the Register of Data Exclusivity Granted in Malaysia, refer to:
Register of Data Exclusivity Granted in Malaysia (New Drug) and *Register of Data Exclusivity Granted in Malaysia (Second Indication)*

2. HOW TO APPLY

An application for Data Exclusivity (DE) can be made via a Letter of Intent (LOI) in conjunction with the:

a) Application for registration of a new drug product containing a New Chemical Entity; or
b) Application for a Second Indication of a registered drug product.

The LOI shall be addressed and submitted manually to the Director of NPRA.

The application must comply with all terms and conditions stated in Directive No. 2, 2011: *Arahan Bagi Melaksanakan Data Eksklusiviti Di Malaysia.*

The following details are extracted from Directive No. 2, 2011 on Data Exclusivity (DE) issued by the Director of Pharmaceutical Services under Regulation 29, Control of Drugs and Cosmetics Regulations 1984, *Bil. (11) dlm. BPFK/PPP/01/03 Jld. 1* (28 February 2011).

3. APPLICABILITY AND DATE OF COMING INTO FORCE

Applicable to:

i) New drug product containing a new chemical entity; and
ii) Second indication of a registered drug product.

New drug product containing any new chemical entity means a product that contains an [1]**active moiety** that has not been registered in accordance with the provisions of the CDCR 1984.

[1]**An active moiety** is defined as the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds) or other non-covalent derivative (such as a complex, chelate or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

Second indication for a registered drug product means a single or cluster of therapeutic indications applied subsequent to the first indication(s) approved at the point of registration of the product. The application for approval of the second indication contains reports of new clinical investigations other than bioavailability studies.

4. GRANT OF DATA EXCLUSIVITY

Any person may apply for Data Exclusivity. Such application shall be made upon submission of documents to the Director of Pharmaceutical Services for the:

a) Registration of a new drug product containing a new chemical entity; or
b) Approval for second indication of a registered drug product.

An application for Data Exclusivity shall only be considered if the application in Malaysia for:

a) New drug product containing a new chemical entity is made within eighteen (18) months from the date the product is first registered or granted marketing authorization; AND

   Granted Data Exclusivity/ Test Data Protection in the country of origin or in any country, recognized and deem appropriate by the Director of Pharmaceutical Services.

b) Second indication of a registered drug product is made within twelve (12) months from the date the second indication is approved; AND
   Granted Data Exclusivity/ Test Data Protection in the country of origin or in any country, recognized and deemed appropriate by the Director of Pharmaceutical Services.

Before the Data Exclusivity is granted:

a) The applicant of a new drug product containing a new chemical entity shall provide to the Director of Pharmaceutical Services the undisclosed, unpublished and non-public domain pharmaceutical test data, the origination, of which involves a considerable effort; OR

b) The applicant for a second indication of a registered drug product shall provide to the Director of Pharmaceutical Services, the reports of new clinical investigations other than bioavailability studies, conducted in relation to the second indication and the origination of which has involved considerable effort.

The Director of Pharmaceutical Services shall decide on whether the application will be granted the Data Exclusivity. The period of the Data Exclusivity granted shall be made on a case to case basis.

The period of the Data Exclusivity **shall not** be more than:

a) Five (5) years for a new drug product containing a new chemical entity; and
b) Three (3) years for a second indication of a registered drug product. The period of Data Exclusivity is for the data concerning the second indication only.

Calculation of the period of Data Exclusivity:

a) For a new drug product containing a new chemical entity, the period of Data Exclusivity shall be calculated from the date the product is first registered or granted marketing authorization AND granted Data Exclusivity/ Test Data Protection in the country of origin or in any country recognized and deemed appropriate by the Director of Pharmaceutical Services.

b) For a second indication of a registered drug product, the period of Data Exclusivity shall be calculated from the date the second indication is first approved AND granted Data Exclusivity/ Test Data Protection in the country of origin or in any country recognized and deemed appropriate by the Director of Pharmaceutical Services.

5. CONSIDERATION OF OTHER APPLICATIONS UPON THE GRANT OF DATA EXCLUSIVITY

For a registered new drug product containing a new chemical entity, registration of any other drug product where the active moiety is in all respect the same as the active moiety in the registered drug product which has been granted Data Exclusivity in Malaysia can be considered if:

a) The applicant provides undisclosed, unpublished and non-public domain pharmaceutical test data, the origination of which involves a considerable effort to demonstrate the quality, safety and efficacy if the drug product submitted for registration; OR

b) The applicant has obtained consent in writing for right of reference or use of the test data from a person authorised by the owner of the registered new drug product containing a new chemical entity.

6. NON-APPLICATION OF DATA EXCLUSIVITY

Nothing in the Data Exclusivity shall:

a) Apply to situations where compulsory licences have been issued or the implementation of any other measures consistent with the need to protect public health and ensure access to medicines for all; or
b) Prevent the Government from taking any necessary action to protect public health, national security, non-commercial public use, national emergency, public health crisis or other extremely urgent circumstances declared by the Government.

7. APPEAL

Any person aggrieved by the decisions of the Director of Pharmaceutical Services may make a written appeal to the Minister within fourteen (14) days from the date the decision is made known to him and any decision of the Minister made on an appeal shall be final.

A person making an appeal may submit any supporting data or documents to the Director of Pharmaceutical Services not later than:

a) 120 days for application of new drug products containing any new chemical entity; or
b) 90 days for the application for second indication of a registered drug product.

Please refer also to **Appendix 24: Appeal**.

APPENDIX 11

REGULATORY CONTROL OF ACTIVE PHARMACEUTICAL INGREDIENTS (APIs)

CONTENT:

1. INTRODUCTION

2. DEFINITION
- 2.1 Definition of Active Pharmaceutical Ingredient (API)
- 2.2 Definition of main API manufacturer

3. SCOPE

4. PROCEDURE FOR SUBMISSION AND RELATED INFORMATION
- 4.1 Required Information
- 4.2 Online Submission
- 4.3 Processing Fee
- 4.4 Other Considerations

5. TYPES OF API SUBMISSION
- 5.1 Option 1: Drug Master File (DMF)
- 5.2 Option 2: Certificates of Suitability (CEP)
- 5.3 Option 3: Part II-S ACTD

6. OTHER RELATED INFORMATION
- 6.1 Stability Data
- 6.2 Good Manufacturing Practice (GMP)
- 6.3 Atypical API
- 6.4 New Registration Application using Same Source of Approved API
- 6.5 Product Registration Application Referencing to a Drug Master File (DMF) Previously Submitted to NPRA

7. REGULATORY CONTROL OF API IN REGISTERED PRODUCT

8. REFERENCES AND GUIDELINES

1. INTRODUCTION

1.1. A significant part of the quality of a finished product is dependent on the quality of the Active Pharmaceutical Ingredient (API) used for its formulation. Thus, a proper system of qualification of suppliers is necessary to ensure a constant sourcing of API of appropriate quality and to safeguard the public health interests. This will be done through standardized quality assessment and inspection procedures.

1.2. The National Pharmaceutical Regulatory Agency (NPRA) under the purview of the Ministry of Health Malaysia has introduced mandatory control of API as part of the requirements in the product registration application.

1.3. The implementation began with voluntary submission for New Drug Product in April 2011 and followed by:

Phase 1	New Drug Products (January 2012)
Phase 2	Scheduled Poison a) New Application (Generic Product): - i. Parenteral Dosage Form : 1 July 2014 ii. Oral Dosage Form : 1 July 2016 iii. Others : 1 July 2018 b) Registered Product (Pharmaceutical products containing Scheduled Poison): All Dosage Form: Expire on 1 January 2020 onwards *refer to No. 7 of this document.
Phase 3	Generic Product NOT containing Scheduled Poison (to be determined)

References:

i) *Bil. (12) dlm. BPFK/PPP/01/03 Jld.1* (17 March 2011)
ii) *BPFK/PPP/07/25 (7)* (16 January 2014)
iii) *Bil. (11) dlm. BPFK/PPP/01/03 Jld.3* (27 June 2014)

1.4 The procedure for control of API established by the NPRA is based on the following principles:

- A general understanding of the production and quality control activities of the manufacturer;
- Assessment of API data and information, including changes and variations, submitted by the product registration holder (PRH)/API Manufacturer. These data should include the manufacturing process, material specifications and test data and results;

- Assessment of the manufacturing site(s) for consistency in production and quality control of raw materials, with specific emphasis on key raw materials and API during and after purification through compliance with Good Manufacturing Practice (GMP);
- Random sampling and testing of API (post-marketing surveillance);
- Handling of complaints and recalls; and
- Monitoring of complaints from other agencies and countries.

1.5. This document is intended to provide guidance regarding the requirements to be included for API in the quality part of the product dossier (Part II-S).

2. DEFINITION

2.1 Definition of Active Pharmaceutical Ingredient (API)

API refers to any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when used so, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body (*WHO Technical Report Series No. 970, 2012*).

2.2 Definition of Main API Manufacturer

Main API Manufacturer refers to the manufacturer involved in the final API manufacturing process and responsible for batch release.

3. SCOPE

3.1. This guideline encompasses the final API of new products for registration and current/existing registered products. This is applicable to all pharmaceutical products (excluding biologic products, traditional products, veterinary products, health supplement products and products for export only (FEO)) both locally manufactured and imported.

3.2. For biological active substances, refer to the relevant guidelines available for Biologics.

3.3. Premixing of API is part of the product manufacturing process; therefore, information on premixed API should be submitted under Part II-P. Submission for Part II-S solely includes information on API only.

3.4. Separate registration of the API is not a requirement for the purpose of product registration. However, the required technical documentation pertaining to each API should be submitted with the new product registration application.

4. PROCEDURE FOR SUBMISSION AND RELATED INFORMATION

The API information can be submitted to NPRA through one of the following three options:

- Option 1: Drug Master File (DMF) procedure; or
- Option 2: Certificate of Suitability of the European Pharmacopoeia (CEP); or
- Option 3: Part II-S ACTD

4.1 Required Information

4.1.1 Document required for each option of API Information submission are summarized in table 1:

Table 1:
Summary of Document Required for API Information Submission:

Option	Documents required
Option 1 (DMF)	• Part II-S (Open Part) via the online system • DMF (both open and closed part) shall be submitted by DMF holder in electronic copy (CD/DVD) directly to the NPRA to maintain confidentiality of the contents. • Letter of Access (LOA) • Current GMP certificate or any other evidence of GMP compliance from a regulatory authority; • See Section 5 for details
Option 2 (CEP)	• Part II-S (Open Part) via the online system (as deemed appropriate) • CEP with written statement • See Section 6 for details
Option 3 (ACTD)	• Full details of Part II-S ACTD via the online system. • Current GMP certificate or any other evidence of GMP compliance from a regulatory authority; • See Section 7 for details

*For GMP requirement refer to No. 6.2 of this document.

4.1.2 Separate API information must be provided for each API for:

- Finished product containing more than one (1) API
- API from different manufacturing site
- API from different synthesis route

4.1.3 The NPRA reserves the right to request for **any** additional information about the API when deemed appropriate.

4.2 Online Submission

4.2.1 All Part II-S information should be submitted through the online QUEST system [except for Closed part of Drug Master File (DMF) for DMF option]. Refer to **'Help Button'** in QUEST for assistance during online submission.

4.2.2 Separate Part II-S information (in the same product registration application form) shall be submitted when:

- A finished product contains more than one (1) API
- An API is manufactured from more than one (1) manufacturing site
- An API is manufactured using more than one (1) synthesis route

4.2.3 Select the **correct API manufacturer** (with the exact name & address) from QUEST database and ascertain your selection. Changes to the name or address of an API manufacturer are NOT possible once a saved form is created.

4.2.4 There are three options for Part II-S information submission. Refer to No.5 of this document.

4.2.5 Change of submission option or change or addition of API manufacturer is NOT allowed once the screening approval is obtained.

4.2.6 The Administrative Procedure for Regulatory Control of Active Pharmaceutical Ingredient (API) is available on NPRA website (refer to 8.1).

4.3 Processing Fees

Fees are not required as the API application is already incorporated in the application for product registration.

4.4 Other Considerations

In the spirit of harmonisation of regulatory activities and optimisation of efficient assessment, NPRA may take into consideration the evaluation of relevant API by the regulatory authorities of reference countries (Australia, Japan, France, Switzerland, United Kingdom, Canada, Sweden, and the United State of America) and, other PIC/S countries and World Health Organization (WHO).

5. TYPES OF API SUBMISSION

5.1 Option 1: Drug Master File (DMF)

5.1.1 The Drug Master File (DMF) is a document that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more API.

5.1.2 DMF is generally created to allow an authorized party other than the holder of the DMF to refer the DMF without disclosing the contents of the file to any other party.

5.1.3 The ICH M4Q Technical Guideline and ASEAN Common Technical Requirements (ACTR)/ ACTD provide details on the information to be included in the API sections of an application dossier.

5.1.4 The DMF is divided into two parts, namely the Open (or PRH's) part and the Closed (or restricted) part.

5.1.5 The documents required for an online application making a reference to a DMF are as follows:

From the PRH: Open part of the DMF, as part of the submitted product dossier contains most of the information in Part II-S – (i.e. sections S1, S2.1 and S3 to S7 excluding S2.2 – S2.6):		
	S1	**General Information**
		1.1 Nomenclature 1.2 Structure 1.3 General Properties
	S2	**Manufacture**
		2.1 Manufacture(s)/Site of Manufacture ***ALL** manufacturers involved in manufacturing process of API, including intermediate manufacturers and milling/ micronisation sites.
	S3	**Characterisation**
		3.1 Elucidation of Structure and other Characteristics 3.2 Impurities
	S4	**Control of API/Drug Substance**
		From API manufacturer: 4.1 Specification of API 4.2 Analytical Procedures 4.3 Validation of Analytical Procedures 4.4 Batch Analysis-minimum three batches 4.4.1 Certificate of Analysis (COA)-minimum two batches. 4.5 Justification of Specification **From finished product manufacturer:** 4.1 Specification of API 4.4.1 Certificate of Analysis (COA)-minimum two batches
	S5	**Reference Standards or Materials**
		From API manufacturer and finished product manufacturer

	S6	**Container Closure System**
	S7	**Stability**
		Refer to No. 6 of this document
	S8	**Drug Master File (DMF)**
		8.1 Letter of Access 8.2.1 Name of DMF Holder 8.2.2 Address of DMF Holder 8.2.3 Phone No. of DMF Holder 8.2.4 Email address of Contact Person-DMF Holder
	S9	**Certificate of GMP for API Manufacturer**
		9.1 Attach a valid copy of GMP Certificate 9.2 GMP Issuing Body 9.3 Date of Issue of Certificate of GMP 9.4 Date of Expiry of Certificate of GMP
	S10	**Other Supporting Document** e.g. Attachment for S2.1 Manufacturer and compendial monograph
From the API Manufacturer: The Complete DMF (open part AND closed part); S1-S7. The closed part contains the confidential information in section Part II-S (i.e. section S2.2 -S2.6);		
	S2	**Manufacture** 2.1 Manufacture(s)/ Site of Manufacture 2.2 Description of Manufacturing Process and Process Controls 2.3 Control of Materials 2.4 Controls of Critical Steps and Intermediates 2.5 Process Validation and/or Evaluation 2.6 Manufacturing Process Development

5.1.6 Summary of Required Documents for API Information in Product Registration Application is available for download on NPRA website (refer to 8.1).

5.1.7 The PRH is responsible to ensure that the complete DMF (i.e. both the Open part and the Closed part) is submitted to NPRA via electronic copy (e.g. CD/DVD/e-DMF) together with a Letter of Access (LOA):
The Letter of Access from API Manufacturer/ holder of the DMF authorizes the NPRA to refer to the DMF, in support of the application for a finished product. Thus, the Letter of Access must state the following:

- The name of the finished product (product name, dosage form and product strength) to be registered
- DMF version number (Open part & Closed part)
- Contact person for DMF correspondence (name and email address)

- The PRH responsible for finished product registration
- A declaration that both the PRH and the NPRA shall be notified of any change in the API specification or in the manufacturing process that will likely affect the product's quality or safety.

5.1.8 The information contained in the closed part of the DMF will be regarded as confidential and will only be evaluated in support of the applications mentioned in the Letter of Access. The confidential information will not be disclosed to any third party without a written authorization from the API Manufacturer.

5.1.9 A BPFK/NPRA DMF number will be assigned to the DMF during product registration evaluation. For future correspondences, the PRH and the API Manufacturer should make a reference to the BPFK/NPRA DMF number. The NPRA will directly contact API Manufacturer for any correspondence pertaining to API information in closed part.

5.1.10 API Manufacturer is responsible to maintain and update the DMF. The PRH should file a variation once they are notified with the changes to the DMF.

- Any change or addition, including a change in authorization related to specific PRH, shall be submitted to the NPRA in duplicate and adequately cross-referenced to previous submission(s). The reference should include the date(s), volume(s), section(s), and/or page number(s) affected.
- Should any change to a DMF is necessary, the API Manufacturer shall notify each affected PRH who has referenced the DMF of the pertinent change. Such notice should be provided well before making the change in order to permit the PRH to supplement or amend any affected application(s) as needed.

5.2 Option 2: Certificates of Suitability (CEP)

5.2.1 CEP stands for certification of suitability of European Pharmacopoeia monographs/Certificate of Pharmacopoeia.

5.2.2 The CEP is a document that used to demonstrate the purity of a given API produced by a given manufacturer is suitably controlled by the relevant monograph(s) of the European Pharmacopoeia. By demonstrating grant a CEP for given API, the suppliers of the API can prove such suitability to their pharmaceutical industry clients and the NPRA.

5.2.3 The PRH should submit a copy of the most current CEP including all annexes, together with the following:

- A written assurance that no significant changes in the manufacturing methods or processing have taken place following the granting of the certificate or its last revision and;
- A declaration from the API Manufacturer that the PRH and the NPRA shall be notified of any future change in the API specifications or in the manufacturing process that will likely affect the product's quality or safety.

Note: *All such written statements must state the name of the finished product (product name, dosage form and product strength) to be registered and the PRH shall responsible for finished product registration.*

5.2.4 The PRH should provide the following information in the online submission:

S(i-iii)	**Certificate of Suitability (CEP)**
	i) A copy of the most current CEP including all annexes ii) Written Statement** ** Written statement is: • A written assurance that no significant changes in the manufacturing methods or processing have taken place following the granting of the certificate or its last revision and; • A declaration from the API Manufacturer that the PRH and the NPRA shall be notified of any future change in the API specifications or in the manufacturing process that will likely affect the product's quality or safety. • All such written statements must state the name of the drug product (product name, dosage form and product strength) to be registered and the PRH shall responsible for finished product registration.)
S1	**General Information**
	1.1 Nomenclature 1.2 Structure 1.3 General Properties Discussions on any additional applicable physicochemical and other relevant API properties that are not controlled by the CEP and Ph.Eur. monograph, e.g. solubilities and polymorphs as per guidance in this section
S2	**Manufacture**
	2.1 Manufacture(s)/Site of Manufacture ***ALL** manufacturers involved in manufacturing process of API, including intermediate manufacturers and milling/micronisation sites. 2.5 Process Validation and/or Evaluation In the case of sterile API, data on the sterilization process of the API, including validation data, should be included in the product dossier (S 2.5)
S3	**Characterisation**
	3.1 Elucidation of Structure and other Characteristics Studies to identify polymorphs (exception: where the CEP specifies a polymorphic form) and particle size distribution, where applicable, as per guidance in this section
S4	**Control of API/Drug Substance**
	From API manufacturer: 4.1 Specification of API

	Note: Specification should include all tests and limits of the CEP and Ph.Eur. monograph and any additional tests and acceptance criteria that were not controlled in the CEP and Ph.Eur. monograph, such as polymorphs, impurities and/or particle size distribution. 4.2 Analytical Procedures* 4.3 Validation of Analytical Procedures* 4.4 Batch Analysis-minimum three batches 4.4.1 Certificate of Analysis (COA)-minimum two batches. 4.5 Justification of Specification *for any methods used by the API manufacturer and <u>in addition</u> to those in the CEP and Ph.Eur. monograph. **From finished product manufacturer:** 4.1 Specification of API 4.4.1 Certificate of Analysis (COA)-minimum two batches.
S5	**Reference Standards or Materials**
	From API manufacturer <u>AND</u> finished product manufacturer
S6	**Container Closure System** <u>Exception:</u> where the CEP specifies a container closure system and the PRH declares to use the same container closure system.
S7	**Stability**
	<u>Exception:</u> where the CEP specifies a **re-test period** that is the same as or of longer duration, and **storage conditions** which are the same or higher temperature and humidity as proposed by the PRH.
S10	**Other Supporting Document** e.g. Attachment for S2.1 Manufacturer and compendial monograph

5.2.5 Summary of Required Documents for API Information in Product Registration Application is available for download on NPRA website (refer to 8.1).

5.2.6 The NPRA reserves the right to request for **any** additional information about the API when deemed appropriate.

5.2.7 The PRH is responsible to submit the latest CEP updates, with annexes, as soon as it is available from the API Manufacturer.

5.3 Option 3: Part II-S ACTD

5.3.1 Information on the API sections (ACTD Part II-S: S1-S7), including full details of chemistry, manufacturing process, quality controls during manufacturing and process validation for the API, shall be submitted in the product dossier.

5.3.2 The ICH M4Q Technical Guideline and ASEAN Common Technical Requirements (ACTR)/ ACTD provide details on the information to be included in the online submission:

S1	**General Information**
	1.1 Nomenclature 1.2 Structure 1.3 General Properties
S2	**Manufacture**
	2.1 Manufacture(s)/ Site of Manufacture ***ALL** manufacturers involved in manufacturing process of API, including intermediate manufacturers and milling/micronisation sites. 2.2 Description of Manufacturing Process and Process Controls 2.3 Control of Materials 2.4 Controls of Critical Steps and Intermediates 2.5 Process Validation and/or Evaluation 2.6 Manufacturing Process Development
S3	**Characterisation**
	3.1 Elucidation of Structure and other Characteristics 3.2 Impurities
S4	**Control of API/Drug Substance**
	From API manufacturer: 4.1 Specification of API 4.2 Analytical Procedures 4.3 Validation of Analytical Procedures 4.4 Batch Analysis-minimum three batches 4.4.1 Certificate of Analysis (COA)-minimum two batches. 4.5 Justification of Specification **From finished product manufacturer:** 4.1 Specification of API 4.4.1 Certificate of Analysis (COA)-minimum two batches.
S5	**Reference Standards or Materials**
	From API manufacturer <u>AND</u> finished product manufacturer

S6	**Container Closure System**
S7	**Stability**
	Refer to No. 6 of this document
S9	**Certificate of GMP for API Manufacturer**
	9.1 Attach a valid copy of GMP Certificate 9.2 GMP Issuing Body 9.3 Date of Issue of Certificate of GMP 9.4 Date of Expiry of Certificate of GMP
S10	**Other Supporting Document** e.g. Attachment for S2.1 Manufacturer and compendial monograph

5.3.3 Summary of Required Documents for API Information in Product Registration Application is available for download on the NPRA website (refer to 8.1).

6. OTHER RELATED INFORMATION

6.1 Stability Data

6.1.1 Current stability test data for an API shall be provided, for at least three (3) primary batches. These data shall include:

- The type of stability study and stability protocol
- API name, API manufacturer, packaging particular
- Batch details (e.g., batch number, date of manufacture, batch size)
- The general test methodology (e.g., duration of study, storage conditions of temperature and humidity, list of relevant testing, testing frequency, etc.);
- Proposed retest period or shelf-life;
- Proposed storage condition;

  A storage temperature must be specified, e.g.:
  - Do not store above 25 °C
  - Do not store above 30 °C
  - Store in a refrigerator (2 °C to 8 °C)
  - Store in freezer

  Other special storage condition, e.g.:
  - Protect from light
  - Protect from moisture
- The analytical test methods (e.g., assay method of quantitation, determination of degradation products, moisture etc.) with reference;
- Validation of test methods;
- Specification;
- Results of tests; and,
- Conclusions.

6.1.2 In circumstances where an API retest period has not been established and complete long-term stability data is not available at the time of submission, the minimum stability data required are as follows:

- At least twelve (12) months of long-term data and six (6) months of accelerated data on at least three (3) primary batches of the API;
- The batches should be at least pilot scale-sized and manufactured by a method that simulates the final commercial process.

  * In view of this, the re-test date may be extended beyond the end of long-term studies, which can be extrapolated not more than twelve (12) months covered by the long term data.

  A letter of commitment (to provide complete long-term stability data when study is completed/when requested) shall be submitted.

6.1.3 Where the API is sourced from multiple sites or from different route of synthesis, stability data from each source shall be provided.

6.1.4 NPRA may request for additional stability data if deemed necessary for the evaluation of the application.

6.1.5 Stability data is not required where the CEP specifies a re-test period and storage condition that is the same as stated in the online submission.

6.2 Good Manufacturing Practice (GMP)

6.2.1 The GMP compliance evidence accepted for main API manufacturer (refer to definition at No. 2 of this document) are:

a) GMP Certificate or GMP Inspection Report issued by:
   i. Pharmaceutical Inspection Co-Operation Scheme (PIC/S) Participating Authorities or;
   ii. World Health Organization (WHO) or;
   iii. Drug Regulatory Authority

6.2.2 Manufacturers involved in the manufacturing of **API intermediate** should be able to provide GMP compliance evidence below:

a) GMP Certificate or GMP Inspection Report issued by:
   i. PIC/S Participating Authorities or;
   ii. World Health Organization (WHO) or;
   iii. Drug Regulatory Authority or;
b) Self-declaration from competent person of API Intermediate Manufacturer (refer to *template letter GMP_CP_V1* at NPRA website) or;
c) Declaration from Qualified Person (QP) (for EU countries)

6.2.3 When an atypical API (e.g. excipient, food additive or cosmetic ingredient) is used as an active ingredient in pharmaceutical products, the GMP compliance evidence accepted are:

a) GMP Certificate or GMP Inspection Report issued by:
   i. PIC/S Participating Authorities or;
   ii. World Health Organization (WHO) or;
   iii. Drug Regulatory Authority or;

b) Self-declaration from competent person from Finished Product (FPP) Manufacturer whereby the supplier of atypical API is an approved supplier according to the FPP manufacturer's quality management system [refer to *template Letter_AAPI_V1* at NPRA website (refer to 8.1)].

6.2.4 NPRA reserves the right to determine the acceptability of any GMP compliance evidence.

6.3 Atypical API

6.3.1 Atypical API is excipient, food additive or cosmetic ingredient used as an active ingredient in pharmaceutical products. These substances are known to have lower risk and widely used outside of the pharmaceutical industry, which have meet recognized quality standards, as atypical API for the purpose of this guidance.

6.3.2 A list of Atypical API and its regulatory requirement are outlined in *Guidance Notes for API Information* (refer to 8.1). This list is not meant to be exhaustive and will be reviewed by NPRA from time to time. Should a risk to health be identified, NPRA shall take appropriate compliance and enforcement action proportional to the risk.

6.3.3 It is important to note that each lot or batch of the atypical API shall be, prior to its use in manufacturing process of the finished pharmaceutical products, be tested against and comply with the specifications established by the finished product manufacturer for that atypical API.

6.3.4 Finished product manufacturer (and PRH) are responsible for ensuring products in domestic commerce are safe, suitable and of purported quality.

6.4 New Product Registration Application Using Same Source of Approved API

6.4.1 **Approved API** refers to an API (in a registered product) regulated and approved following the implementation of Directive on Regulatory Control of API in Malaysia dated 17 March 2011.

6.4.2 Same Source of Approved API means the new product registration application is using the same API, which is manufactured by the same API Manufacturer, with the same API

synthetic route as the approved API. This new submission shall be made by the same PRH through the same Part II-S submission option.

6.4.3 The PRH should keep the content of their dossier updated with respect to the actual synthesis/manufacturing process. The quality control methods should be kept in line with the current regulatory and scientific requirements. Where there are changes affecting an approved API in a registered product that requires variation application, the variation application shall be made and approved for every affected registered product prior to submission of a new product registration containing an Approved API.

6.4.4 The PRH is required to declare that the quality of the API, with respect to the methods of preparation and control, has been regularly updated by variation procedure to take account of technical and scientific progress. The PRH shall also declare that no changes have been made to the API other than those approved by the NPRA.

6.4.5 In cases where some minor textual changes have been introduced, and without affecting the major content of the dossier, the PRH shall be able to provide a summary of changes made to previously approved dossier compared to current dossier. NPRA will review the changes introduced and may consider to accept or reject the dossier as an Approved API.

6.4.6 Template for Declaration Letter for An Approved API in New Product Registration Application is available on NPRA website.

6.5 Product Registration Application Referencing to a Drug Master File (DMF) Previously Submitted to NPRA

6.5.1 A Drug Master File (DMF) is a submission used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of an API, in support of a product registration application.

6.5.2 A complete DMF (containing both closed part & open part information) shall be submitted by DMF Holder to NPRA in an electronic copy (CD/DVD/USB/e-DMF) with a Letter of Access (LoA) permitting NPRA and local product registration holder (PRH) to reference the DMF.

6.5.3 DMF holders should send a copy of complete DMF in CD/DVD/USB together with a LoA directly to Head of New Drug Product Section / Generic Medicine Section, Centre of Product and Cosmetic Evaluation, NPRA.

6.5.4 The LoA should include the following:

a. Name of DMF holder
b. Name and address of API manufacturing facility
c. DMF version number (for Applicant's part and Restricted part)
d. Name of the finished product (product name, dosage form and product strength
e. Local product registration holder (PRH) responsible for product registration

f. A declaration that the local PRH and NPRA shall be notified of any changes in the API specification or in the manufacturing process that will likely affect the product's quality or safety
g. Name and email address of person(s) to be contacted for additional information
h. Signature of authorizing official

6.5.5 The DMF holder should send a copy of the **LoA and the open part of DMF** to the dedicated PRH, who is authorized to incorporate by reference the API information contained in the DMF. The PRH is required to upload the API information (open part) on QUEST3+ during registration application.

6.5.6 DMFs received will be kept safe at NPRA. The information in a DMF will only be reviewed when a PRH submit a product registration application referencing to the DMF (with a LoA). If there are deficiencies found in the confidential information provided in a DMF, NPRA will send a letter describing the deficiencies to the DMF holder. At the same time, NPRA will notify the PRH that additional closed part information is needed in the supporting DMF. Deficiencies related to open part of the DMF will be requested via QUEST3+.

6.5.7 In situations where the DMF holder has previously submitted a complete DMF to NPRA and wished to reference the **same version of DMF** with another PRH, DMF holder is **only** required to supplement with a **LoA**. The new LoA shall be sent to NPRA via email to apiscreening@npra.gov.my. Information below shall be provided as reference:

a. Indication for submission: new product application/ renewal/ variation
b. Name of Product
c. Name of API
d. Name of PRH
e. Name of DMF Holder
f. Name and Address of API Manufacturer
g. DMF Version Number (shall be the **same** as previously submitted and shall not more than **3 years** from last submission)

6.5.8 In situations where the DMF holder has previously submitted a complete DMF to NPRA and wished to reference an **updated version of the DMF**** with another PRH, DMF holders should provide information **in addition** to above:

a. Declaration of no change; or
b. Table of comparison to describe changes / differences between the previous and current version

**newer version of the DMF (with minor changes) for the same API salt/ form/ grade/ standard with the same API manufacturing process and synthesis route, at the same manufacturing site

6.5.9 The list of DMF received by NPRA will not be disclosed to PRH for confidentiality concerns. The action of **referencing a DMF** with more than one PRH **shall be initiated by the DMF holder** and as noted, the incorporation by reference must be accompanied by a copy LoA.

7. REGULATORY CONTROL OF API FOR REGISTERED PRODUCT

7.1 This section is applicable for registered products containing Scheduled Poison in ALL dosage forms with the expiration of the registration period starting 1 January 2020.

7.2 At the point of writing, NPRA has identified anti-infective API as the selected category for assessment purposes. This category was selected based on current public health needs and risk-based approach, which may be extended to other categories from time to time.

7.3 The PRH shall prepare all required Part II-S document. This information shall be uploaded to QUEST between 12 to 15 months prior to expiry of product registration.

a. Submission by DMF option- complete DMF (both open & closed part) shall be submitted in electronic copy (preferably in compact disc) together with a Letter of Access and Cover Letter. This document shall reach NPRA before submission of Form RegA2. Open part information shall also be uploaded to QUEST.
b. Submission by ACTD or CEP option- all documents shall be uploaded to QUEST.

7.4 Administrative Procedure for Regulatory Control of Active Pharmaceutical Ingredient (API) In Registered Product Containing Anti Infective API is available on NPRA website (refer to 8.1).

7.5 Once all required Part II-S document are ready for updating, PRH shall fill and submit *Application Form for Section S Revision for Products (Anti-Infectives) Registered Before the Implementation of Directive on Regulatory Control of API (Form RegA2).* Form RegA2 is an online form available on NPRA's website.

7.6 All submissions will be screened for eligibility based on product registration expiration date and category of API.

7.7 NPRA will enable "Product Editing" function in QUEST 3+ for the indicated product. PRH will be given strictly 30 calendar days to upload all required Part II-S document. Failure to update complete Part II-S information by the end of the given timeframe will affect product renewal status.

7.8 During assessment, additional information may be requested via email, if necessary.

7.9 For registered products not containing anti-infective API, Part II-S document shall be kept by the PRH. It is not necessary to upload to QUEST.

7.10 For non-anti-infective API, NPRA reserves the right to request for Part II-S documents for full assessment (if deemed necessary). If the outcome of the assessment is unsatisfactory or if there is any doubt in the submitted document, appropriate regulatory action may be taken against the relevant product and/or the status of the product registration will be reviewed for product recall, suspension or revoking of registration status.

8. REFERENCES AND GUIDELINES

8.1 Guidance Note for Active Pharmaceutical Ingredient (API) Information published on NPRA website: *https://npra.gov.my/index.php/en/active-pharmaceutical-ingredient-api-main-page.html*

8.2 Guidelines on the Technical Requirements Related to the Quality of API

The technical requirements related to the quality of API have already been addressed elsewhere, (such as in the ASEAN, WHO, ICH, EDQM and EMA guidelines), and the PRH are advised to refer to these guidelines available at the relevant website such as:

- Guideline on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product (FPP): Quality Part
- Guideline on Active Pharmaceutical Ingredient Master File (APIMF) Procedure.
- The ASEAN Common Technical Dossier (ACTD) For The Registration Of Pharmaceuticals For Human Use Organization Of The Dossier
- The Common Technical Document For The Registration Of Pharmaceuticals For Human Use: Quality – M4Q(R1)
- ICH Q3A (R2) Impurities in new drug substances
- Impurities: Guideline for Residual Solvents Q3C (R6)
- Guideline for Elemental Impurities Q3D(R1)
- Guideline for Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk M7 (R1)
- Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients Q7
- Guideline for Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) Q11
- Certification database for information on Certificates of Suitability (CEPs) granted by the EDQM.

APPENDIX 12

PRIORITY REVIEW

1. Priority review may be granted for new product application (in the category of New Drug Products, Biologics and Generics) which fulfils either one of the following conditions;

   a) Product which is intended for:
      (i) Unmet medical needs (e.g. medicines for rare diseases, new vaccines, etc.) with no treatment options locally available,
      (ii) Life-saving such as for treatment/ prevention of serious medical conditions (e.g. anticancer, antiretroviral, etc.) with no treatment options locally available,
      (iii) Treatment/ prevention in pandemic/ endemic situations, for the interest of public health,
      (iv) Emergency supply/ crucial for treatment purpose according to the current needs in the country,
      (v) Supply to the Ministry of Health Malaysia under circumstances where alternative product with the same active ingredient is unavailable,

   b) Product which involves a change in the formulation due to the decision/ instruction by the Drug Control Authority (DCA), for the purpose of formulation improvement with appropriate scientific justification(s),

   c) New application for products that have been registered with the same active ingredient for which the registration has been cancelled/ withdrawn due to issues other than safety issues. Priority review will be considered based on individual/ case to case basis and involves product that is crucial for treatment purpose.

   d) Product which is the first *generic/ biosimilar product, or the first locally manufactured generic/ biosimilar product.

      **No generic/ biosimilar product has been registered by DCA at point of consideration on granting Priority Review*

      **The priority review status granted based on condition c) shall be cancelled during the duration of product application evaluation, in the event that a same/ similar first generic/ biosimilar product or first locally manufactured generic/ biosimilar product has been approved for registration.*

2. An application for Priority Review should be submitted via a formal letter addressed to the Director of NPRA once the screening has been approved.

3. The approval of Priority Review is subjected to the decision of the Drug Evaluation Committee Meeting upon submission of complete product registration documentation and does not exempt applicant from any product registration requirements.

4. The timeline for evaluation for product granted Priority Review is as below;

No.	**Product Category**	**Duration** (Starting from the date of approval of Priority Review)
(A)	**Full Evaluation**	
1.	New Drug Products	120 working days
2.	Biologics	120 working days
3.	Generics (Scheduled Poison)	100 working days
4.	Generics (Non-Scheduled Poison)	100 working days

APPENDIX 13

DESIGNATION AND REGISTRATION OF ORPHAN MEDICINES

Note: This part shall be read in conjunction with other parts of the DRGD that apply to orphan medicines (where applicable), e.g. re-registration procedure, withdrawal of registration, labeling requirements, post-market surveillance, etc.

Please also refer to Malaysian Orphan Medicines Guideline, FAQ and documents related to orphan medicines available at **www.pharmacy.gov.my**

As defined in the **Malaysian Orphan Medicines Guideline**, an orphan medicine is a medicinal product that is primarily intended to treat, prevent or diagnose a rare disease. Rare disease refers to a life-threatening and/ or chronically debilitating rare condition as listed in the Malaysian Rare Disease List.

1. DESIGNATION OF ORPHAN MEDICINE

The designation of orphan medicine is under the purview of *Bahagian Regulatori Farmasi Negara* (NPRA) through input from the Drug Evaluation Committee (DEC).

2. ELIGIBILITY CRITERIA FOR DESIGNATION OF ORPHAN MEDICINE

The designation of orphan medicine is subject to the following criteria:

a) "A medicine, vaccine or in vivo diagnostic agent that is primarily intended to treat, prevent or diagnose a rare disease"[1]; and

b) No satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorized; or, if such a method exists, the medicinal product must be of significant benefit[2] to those affected by the condition.

[1] Rare disease refers to the diseases listed in the latest Malaysian Rare Disease List.
[2] As defined by European Medicines Agency (EMA), significant benefit means that a medicine produces a clinically relevant advantage or makes a major contribution to patients' care, compared with existing methods to treat the condition. Thus, orphan designation is given to a product that will improve patients' current treatment, having considered what else is available.

3. APPLICATION FOR THE DESIGNATION OF ORPHAN MEDICINE

a) The applicant may submit an application for such designation to the NPRA using the *Orphan Medicine Designation Application Form*.

b) The application can be submitted before a product is registered as a New Chemical Entity or a Biologic product.

c) The information required for an application for orphan medicine designation may include but are not limited to the following:

Product Information

i) Product name
ii) Active ingredient
iii) Strength
iv) ATC Code
v) Pharmaceutical form
vi) Route of administration
vii) Manufacturer name and address
viii) Worldwide regulatory status
ix) Worldwide orphan medicine designation status

Proposed Rare Disease and Condition

i) Proposed indication related to the rare disease
ii) Brief description of the rare disease
iii) Current available method in treating/preventing/diagnosing the rare disease
iv) Justification for this product to be designated as orphan medicine
v) Brief description of the product (details on active ingredient(s), drug type/ class, structure, physical-chemical properties)
vi) Mechanism of action explaining how the product works in relevant disease/ condition

Scientific rationale for the orphan medicine use (The scientific rationale should support a medical plausible basis for the orphan medicine to be effective in treating disease/ condition

i) Please briefly describe the scientific evidence to support safety and efficacy of this product to treat/ prevent/ diagnose the proposed indication related to the rare disease
ii) Tabulated pre-clinical data and clinical data
iii) A brief safety update report

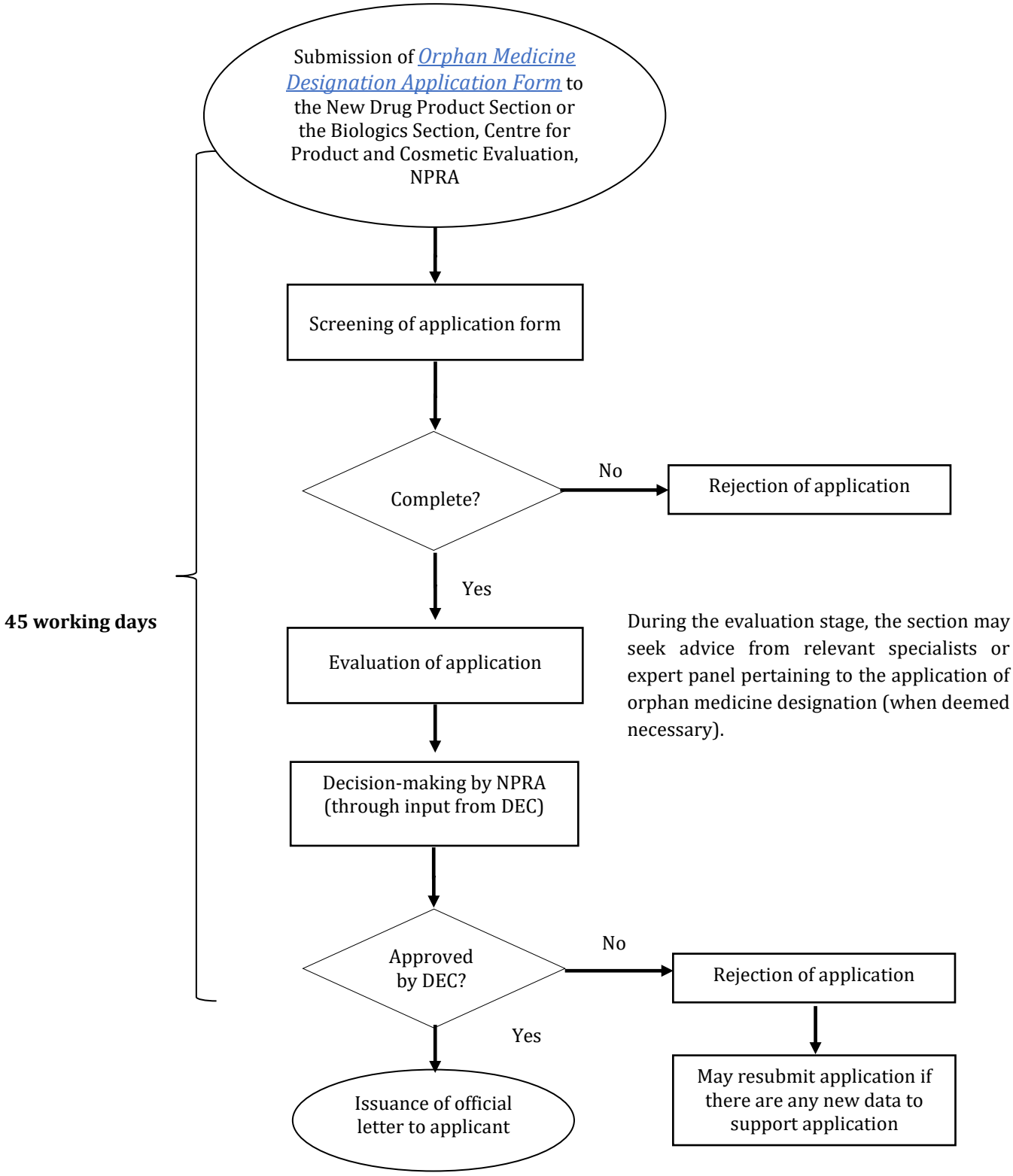
d) A medicinal product that has already been granted an orphan medicine designation in other countries is not automatically designated as an orphan medicine in Malaysia. It is still subject to the decision of NPRA (through input from the DEC).

e) The same medicinal product may also have multiple orphan medicine designations for different rare diseases.

f) NPRA may seek advice/ opinion from relevant experts or representatives from the rare disease society/ patient groups or other key opinion leaders pertaining to the application of orphan medicine designation when deemed necessary.

3.1 APPLICATION WORKFLOW AND PROCEDURE

a) Workflow of ORPHAN MEDICINE DESIGNATION



b) Procedure for ORPHAN MEDICINE DESIGNATION Application

1. **Submission of Orphan Medicine Designation Application Form (refer to 6.) to the New Drug Product Section or the Biologics Section, Centre for Product and Cosmetic Evaluation, NPRA**
   - The applicant can also download the Orphan Medicine Designation Application Form from the **NPRA official website**.
   - The applicant shall submit the completed application form to the relevant section, depending on the product category.
   - The applicant shall submit a separate application form for designation of same orphan medicine to treat a different rare disease (as same medicinal product may be used to treat different rare disease)

2. **Screening of application form**
   - The relevant section shall screen the submitted form (i.e., without the dossier).
   - If the form is found incomplete, the application shall be rejected.
   - A complete application shall be further evaluated.

3. **Evaluation of application**
   - The section may seek advice from relevant specialists or expert panel when deemed necessary. A timeframe of two weeks is allocated for the reply.
   - The section shall prepare an evaluation report to be tabled in the DEC meeting.

4. **DEC Meeting**
   - The DEC shall make the decision to grant the designation of orphan medicine or otherwise.

5. **Issuance of official letter to applicant**
   - The decision of the DEC shall be informed to the applicant via official letter.

3.2 Timeline

The decision of the DEC to grant the designation of orphan medicine or otherwise will be made within **45 working days** upon receipt of application.

3.3 Cancellation of Orphan Medicine Designation

- The NPRA (through input from the DEC) may, at any time and by notice, cancel any orphan medicine designation of an unregistered/registered medicinal product that no longer meets the criteria for such designation.
- However, the registration status of that medicinal product shall remain valid.

4. REGISTRATION OF ORPHAN MEDICINE

The registration requirements, conditions and fees outlined shall be applicable only to **new medicinal products** that have not been registered before.

4.1 Procedure, Fees and Timeline

a) The PRH may proceed to submit an application for the registration of a medicinal product designated as an orphan medicine via the NPRA QUEST online system.

b) The orphan medicine designation letter issued by NPRA shall be submitted as part of the registration dossier via Quest3+ under Part I- Section E (E14. Other Supporting Documents)

c) The medicinal product that has been granted designation as an orphan medicine will be automatically granted **priority review**. Please refer to **Appendix 12: Priority Review**.

The timeline for evaluation for that medicinal product is as below:

No.	Product Category	Duration
1.	New Chemical Entities	120 working days
2.	Biologics	

The timeline shall commence after payment has been confirmed by the PRH (i.e., post-screening approval).

d) Fee for the registration of orphan medicine shall follow the fees stated in the DRGD, according to product category.

4.2 Registration Requirements and Conditions

This part shall be read in conjunction with the other parts in the DRGD that apply to the registration of orphan medicine, e.g., labelling requirement, etc.

For medicinal products (i.e. new chemical entities and biologics), **certain flexibilities** are permitted for their registration as orphan medicine as follows:

No.	Registration Requirements and Conditions	Comparison of Registration Requirements and Conditions	
		Normal Registration Pathway	**Orphan Medicine**
1.	**Substantial efficacy and safety evidence of the product for the proposed indication**	Phase III clinical data is required	Phase II clinical data may be acceptable, depending on justification (e.g. why Phase III trial is not conducted, approved in a DCA reference country and supported by real-world evidence data) and may be subjected to certain approval obligations. These obligations may include but not limited to the following: • the applicant shall complete an identified programme of studies within a time period specified by the competent authority, the results of which shall form the basis of an assessment of the benefit/risk profile. • the medicinal product in question may be supplied on medical prescription only and may in certain cases be administered only under strict medical supervision, possibly in a hospital and in the case of a radio-pharmaceutical, by an authorised person.

No.	Registration Requirements and Conditions	Comparison of Registration Requirements and Conditions	
		Normal Registration Pathway	**Orphan Medicine**
			• the package leaflet and any medical information shall draw the attention of the medical practitioner to the fact that the particulars available concerning the medicinal product in question are as yet inadequate in certain specified respects.
2.	**Stability study data and storage condition of the product according to Zone IVb requirements**	Mandatory (except cold chain products)	Not Mandatory
3.	**Protocol of analysis, analytical method validation and Certificate of Analysis**	Protocol of analysis, analytical method validation and Certificate of Analysis for 3 batches	Protocol of analysis, analytical method validation and Certificate of Analysis for at least 1 batch
4.	**GMP requirements**	a) <u>Foreign Manufacturer:</u> An acceptable GMP evidences (GMP certificate/ GMP inspection report) from any PIC/S Participating Authority (as listed in PIC/S website) or others as stipulated under Directive No.4, 2018 issued by the Senior Director of Pharmaceutical Services.	The product can be manufactured in countries where the health authorities are not the participating authority in the Pharmaceutical Inspection Cooperation/ Scheme (PIC/S). Conditional product registration for the period of 2 years may be granted subjected to an acceptable GMP evidences (GMP certificate/ GMP inspection report) from any PIC/S Participating Authority (as listed in PIC/S website) or others as stipulated under directive

No.	Registration Requirements and Conditions	Comparison of Registration Requirements and Conditions	
		Normal Registration Pathway	**Orphan Medicine**
		Acceptable GMP evidences must be provided prior to product registration. b) <u>Local Manufacturer:</u> GMP inspection by NPRA is mandatory.	No.4, 2018 issued by the Senior Director of Pharmaceutical Services can be provided within the specified time-frame.
5.	**Fees for GMP inspection**	a) <u>Foreign Manufacturer:</u> • Processing fee : RM5,000 • Inspection fee : RM20,000 • Inspection Expenses* **Includes flight ticket, accommodation and other associated expenses*	Fee waiver as follows: a) <u>Foreign Manufacturer:</u> • Processing fee, RM5,000 is waived. • Inspection fee, RM20,000 is waived. ***Note:*** • *Only applicable to foreign manufacturers that produce a registered orphan medicine with no other registered medicinal product produced by the same manufacturer.* • *The fee waiver is granted for a period of 5 years only, and it shall be revised after the specified period.* • *Inspection expenses includes flight ticket, accommodation and other associated expenses still applicable.*

<table>
<tr><th rowspan="2">No.</th><th rowspan="2">Registration Requirements and Conditions</th><th colspan="2">Comparison of Registration Requirements and Conditions</th></tr>
<tr><th>Normal Registration Pathway</th><th>Orphan Medicine</th></tr>
<tr><td></td><td></td><td>b) <u>Local Manufacturer:</u>
<table>
<tr><th>Inspection type</th><th>Charges</th></tr>
<tr><td>Inspection period not more than one (1) working day</td><td>RM1000.00</td></tr>
<tr><td>Inspection period more than one (1) working day</td><td>RM1000.00/ personnel/ working days</td></tr>
<tr><td>Inspection involving more than three (3) inspectors and/or period of more than three (3) working days</td><td>RM10000.00 (Maximum rate)</td></tr>
</table></td><td>b) <u>Local Manufacturer:</u>
Upon registration of the orphan medicine by the Authority, a one-off fee waiver will be given for the subsequent GMP inspection.</td></tr>
</table>

No.	Registration Requirements and Conditions	Comparison of Registration Requirements and Conditions	
		Normal Registration Pathway	**Orphan Medicine**
6.	**Submission of Periodic Safety Updates Report (PSUR)/ Periodic Benefit Risk Evaluation Report (PBRER)**	As part of the post-registration requirement for newly-approved NDP (New Drug Products) and Biologics products in Malaysia, the Product Registration Holder (PRH) is required to routinely submit Periodic Benefit Risk Evaluation Reports (PBRERs) every 6 months for the first 2 years after approval and once a year for the subsequent 3 years. The first PBRER submitted should have a Data Lock Point (DLP) no later than 6 months after approval in Malaysia.	To submit PSUR/PBRER every 6 months for the first 2 years and once a year for the following 3 years. If the requirements cannot be fulfilled, the PRH shall provide an annual safety report, which includes: • A summary (line listing and summary tabulation) report of all the ADR cases received during a period of twelve months. It is preferably submitted in the PRH ADR Summary report format defined in the Malaysian Guidelines on Good Pharmacovigilance Practices (GVP) for Product Registration Holders, First Edition, August 2021. • A review of ongoing clinical study. • Any risk minimisation activities/ programmes requested by other regulatory authorities relevant to the orphan medicine registered. • A description of the investigation plan for the coming year. The first Annual Safety Report should be submitted no later than one month after the anniversary of the registration date in Malaysia.

4.3 Listing of DCA Registered Orphan Medicine

A list of orphan medicine registered with the DCA shall be published on the NPRA website. The list will be updated regularly as and when updates have been made to it.

4.4 Re-registration

The re-registration procedure in DRGD shall apply to the re-registration of an orphan medicine.

4.5 Cancellation of Orphan Medicine Registration

a) The DCA may, cancel any registered orphan medicine that no longer meets the criteria for registration. Cancellation shall only be done during the re-registration of orphan medicine.

b) The cancellation procedure/ details throughout DRGD shall apply to the cancellation of a registered orphan medicine.

5. POST-MARKETING ACTIVITIES

All registered orphan medicine used in Malaysia shall be subjected to post-marketing activities. As such, the Product Registration Holder (PRH) shall be the responsible entity to implement the requirements.

The PRH shall appoint a responsible person in handling post-marketing issues in Malaysia. The details of the current responsible person, such as name, postal address, e-mail address, telephone, and fax numbers shall be provided to the NPRA and are required to be promptly informed if there is any change.

5.1 Surveillance and Product Complaint

The requirement for registered product quality monitoring is described in 21.2 Post-Market Surveillance.

5.2 Pharmacovigilance

The PRH is responsible to ensure that an appropriate system of pharmacovigilance is in place. The PRH shall continuously monitor and determine whether benefits continue to outweigh risks, and to consider the necessity of steps to improve the benefit-risk balance through risk minimization activities. The PRH is responsible and liable for their products on the market and must take appropriate action, when necessary.

For full details on the requirements related to pharmacovigilance, please refer to the Malaysian Guidelines on Good Pharmacovigilance Practices (GVP) for Product Registration Holders, First Edition, August 2021.

i. Management of adverse drug reaction

The PRH shall have in place written procedures describing the handling of all adverse drug reactions (ADRs) related to their products. The system and procedures in place must be adequate for receipt, handling, evaluation and reporting of ADRs to the NPRA within the stipulated timelines stated in the Malaysian Guidelines on Good Pharmacovigilance Practices (GVP) for Product Registration Holders, First Edition, August 2021.

ii. Annual submission of safety reports

Submission of Periodic Safety Updates Report (PSUR)/ Periodic Benefit Risk Evaluation Report (PBRER) every 6 months for the first 2 years and once a year for the following 3 years is required for new drug products and biologic products.

If the requirements cannot be fulfilled, the PRH shall provide an annual safety report, which includes:

- A summary (line listing and summary tabulation) report of all the ADR cases received during a period of twelve months. It is preferably submitted in the PRH ADR Summary report format defined in the Malaysian Guidelines on Good Pharmacovigilance Practices (GVP) for Product Registration Holders, First Edition, August 2021.
- A review of ongoing clinical study.
- Any risk minimization activities or programmes requested by other regulatory authorities relevant to the registered orphan medicine.
- A description of the investigation plan for the coming year.

iii. Emerging Safety Issues

Events/ observations related to a registered orphan medicine may occur, which may have major impact on the risk-benefit balance of the product and/or on patients or public health. They may require urgent attention of the DCA and could warrant prompt regulatory action and communication to

patients and healthcare professionals. These important new evidences should be considered as emerging safety issues.

The PRH shall:

- alert the NPRA of any emerging global safety issue(s).
- submit all relevant safety information such as post-registration study reports and risk management plan as instructed by the NPRA.
- respond promptly to the NPRA on request for additional risk-benefit information of the products concerned.

Any emerging safety issue shall be notified to the NPRA within the stipulated timeline stated in the Malaysian Guidelines on Good Pharmacovigilance Practices (GVP) for Product Registration Holders, First Edition, August 2021.

iv. Safety Communication

Please refer to the Malaysian Guidelines on Good Pharmacovigilance Practices (GVP) for Product Registration Holders, First Edition, August 2021 for further details.

6. ORPHAN MEDICINE DESIGNATION APPLICATION FORM

BAHAGIAN REGULATORI FARMASI NEGARA (NPRA) ORPHAN MEDICINE DESIGNATION APPLICATION FORM		
1. Date of Application:		
2. Information of Applicant (Product Registration Holder, PRH)		
Name of company:	Name of Contact Person:	
Address:	Tel No:	Fax No:
	E-mail address:	
3. Product Information		
Product Name:	Strength:	ATC Code:
Pharmaceutical Form:	Route of administration:	
Active Ingredient:	Strength:	
Manufacturer name and address:		
Worldwide regulatory status:		
Worldwide orphan medicine designation status:		
4. Proposed Rare Disease and Condition		
Proposed Indication related to the Rare Disease: ☐ Treatment ☐ Prevention ☐ Diagnosis		
Brief Description of Rare Disease:		
Current available method in treating/ preventing/ diagnosing the rare disease:		
4. Proposed Rare Disease and Condition (continued)		
Justification for this product to be designated as orphan medicine:		

Brief description of the product (details on active ingredient(s), medicines type/class, structure, physical-chemical properties):
Mechanism of action explaining how the product works in relevant disease/condition:
5. Scientific rationale for the orphan medicine use (the scientific rationale should support a medical plausible basis for the orphan medicine to be effective in treating disease/condition)
Please briefly describe the scientific evidence to support safety and efficacy of this product to treat/prevent/diagnose the proposed indication related to the rare disease:
Tabulated pre-clinical trial and clinical studies(Please enclose together with this form):
A brief safety update report:
6. Declaration of Applicant
i) I hereby declare that all the information and attachment(s) provided are true. ii) I am fully aware of the consequences of rejection of this application if this form is incomplete. …… Name: Company Stamp:

APPENDIX 14

EVALUATION ROUTES

There are four (4) types of methods of evaluation for product registration.

1) **Full Evaluation (Standard Pathway)**

2) **Full Evaluation (Conditional Registration)**
   a) This applies to new registration applications for New Drug Products and Biologics.
   b) At the point of submission, the product must be registered in at least one (1) Drug Control Authority (DCA) reference agency.
   c) A conditional registration does not apply to additional indications submitted post-registration. However, the approval of additional indication with less than comprehensive clinical data may be considered on a case-to-case basis.
   d) A conditional registration is valid for two (2) years. Thereafter, the conditional registration may be renewed two (2) times (with the possibility of two (2) extensions of two (2) years each).
   e) For further details, refer to *Guidelines on Conditional Registration for New Chemical Entities and Biologics*.
   f) For medicinal products or vaccines to be used during disaster:
      - The guideline must be read in conjunction with *Guidance and Requirements on Conditional Registration of Pharmaceutical Products During Disaster*.
      - The validity of conditional registration is one year. Thereafter, the conditional registration may be renewed two (2) times (with the possibility of two (2) extensions of one (1) year each).
      - All registration applications for pharmaceutical products during disaster that fulfil the eligibility conditions shall be automatically given **priority review** status and shall be processed within **70 working days*** from the date the complete application is received. If the product has been conditionally approved or given emergency use authorization or listing by any DCA reference countries or WHO (hereby referred as Recognition Pathway), the time taken for reviewing process would be significantly shortened.

      *Note: The timeline has been revised from 120 working days to **70 working days**.

References:

i. Directive No. 15, 2018, *BPFK/PPP/07/25 (15) Jld.2*: *Direktif Untuk Melaksanakan* Guidelines on Conditional Registration for New Chemical Entities and Biologics (30 May 2018)

ii. Directive No. 18, 2020, *NPRA.600-1/9/13(9)*: *Direktif Berkenaan Pelaksanaan Pendaftaran* Fast-Track *Bersyarat Untuk Produk Farmaseutikal Semasa Bencana* (14 December 2020)

iii. Directive No. 15, 2021, *NPRA.600-1/9/13(25)*: *Direktif Berkenaan Pelaksanaan Pendaftaran Bersyarat Produk Farmaseutikal Semasa Bencana Secara Recognition* (12 July 2021)

3) **Full Evaluation via Abbreviated and Verification Review**

- This applies to New Drug Products and Biologics, including biosimilars.
- Abbreviated Review applies to a product that has been evaluated and approved by one (1) DCA reference agency.
- Verification Review applies to a product that has been evaluated and approved by two (2) DCA reference agencies.
- Refer to *Guidelines on Facilitated Registration Pathway: Abbreviated and Verification Review*. (Effective 1 April 2019)

  Reference: Directive No. 7, 2019, *BPFK/PPP/07/25 (7) Jld.3*: *Direktif Untuk Melaksanakan* Guidelines on Facilitated Registration Pathway: Abbreviated and Verification Review (27 March 2019)

4) **Abridged Evaluation**

Methods of Evaluation According to Product Category:

No.	Product Category	Method of Evaluation	
		Full Evaluation	**Abridged Evaluation**
1.	New Drug Products	√	Not Applicable
2.	Biologics	√	Not Applicable
3.	Generics (Scheduled Poison)	√	Not Applicable
4.	Generics (Non-Scheduled Poison) [or known as OTC]	* All products from this category, unless stated in Abridged Evaluation	Includes, but not limited to the following: • Antiseptics/ skin disinfectants; • Locally acting lozenges/ pastilles; • Topical analgesic/ counter-irritants; • Topical nasal decongestants; • Emollient/ demulcent/skin protectants; • Keratolytics; • Anti-dandruff; • Oral care; • Anti-acne; • Medicated plasters/patch/pad; and • Topical antibacterial.
5.	Health Supplements a) General or Nutritional Claims	Not Applicable	√
	b) Functional Claims (Medium)	Not Applicable	√
	c) Disease Risk Reduction Claims (High)	√	Not Applicable
6.	Natural Products	Not Applicable	√
7.	Natural Products with Therapeutic Claim	√	Not Applicable

APPENDIX 15

REQUIREMENTS FOR FULL EVALUATION AND ABRIDGED EVALUATION

IMPORTANT NOTES:

1. This appendix is for reference purpose only, where applicable. It may not follow the sequence in the online product registration application forms (in QUEST system).
2. Online application forms are available for different product categories.
3. Applicant shall follow and comply with all requirements in the online application forms as well as any supplementary documentation requested by the Authority.

1. FULL EVALUATION (based on ACTD/ ACTR)

No.	Product Category	Part I	Part II	Part III	Part IV
1.	New Drug Products (NCE)	√	√	√	√
2.	New Drug Products (Hybrid)	√	√	Refer to Appendix 3	Refer to Appendix 3
3.	Biologics	√	√	√	√
4.	Generics (Scheduled Poison)	√	√	Not Applicable	Not Applicable
5.	Generics (Non-Scheduled Poison)	√	√	Not Applicable	Not Applicable
6.	Health Supplements: Disease Risk Reduction Claims (High)	√	√	√	√
7.	Natural Products with Therapeutic Claim	√	√	√	√

Part I - Administrative data and product information
Part II - Data to support product quality (Quality Document)
Part III - Data to support product safety (Nonclinical Document)
Part IV - Data to support product safety and efficacy (Clinical Document)

1.1 General Requirements for Full Evaluation

No.	Step I: Product Validation
1.	Product name (Please provide brand name and full product name)
2.	Dosage Form
3.	Active Ingredient(s) a) Active Ingredient Name b) Strength of Active Ingredient (Quantity unit/ dose) c) Source of Active Ingredient (Animal – e.g. Bovine, Porcine, Ovine or Others/ Plant/ Others) d) Form of Active Ingredient e) Remarks (if any)
4.	Excipient(s) a) Excipient name b) Strength of Excipient (Quantity unit/ dose) c) Function of excipient (e.g. absorbent, diluents, bulking agent, coating agent, anti-caking agent etc.) d) Source of excipient e) Remarks (if any)
5.	Is there any source of ingredients derived from animal origin, including active ingredient? (Yes/ No) If yes, please declare the origin
6.	Manufacturer (Name and Address)
7.	Is there any contract manufacturer involved? (Yes/ No)
8.	Is the product a second source product? (Yes/ No) If yes, please provide: a) Letter of declaration stating that this product is a second source product b) Registration number and product name of the first source
9.	Is there any repacker/ packer involved? (Yes/No)
10	Is the product manufactured for export only? (Yes/No)
11.	Is the product under patent protection? (Yes/No) If yes, please provide: a) Patent protection b) Filling date

No.	Step I: Product Validation
	c) Grant date d) Patent statement
12.	Is this an imported product? (Yes/ No)
13.	Does this product containing any premix? (Yes/ No) a) State your premix form b) Manufacturer name c) Manufacturer address d) Certificate of Good Manufacturing Practice (GMP) e) Formulation f) Manufacturing Process g) Specification of Analysis h) Certificate of Analysis (CoA)
14.	Is this a replacement product? (Yes/ No) If yes, please provide: a) Letter of Declaration stating that this product is a replacement product b) Registration number and product name of the replaced product
15	Does this product need priority review? (Yes/ No) If yes, please provide: a) Application letter b) Priority review status c) Date of grant
16	Request for data exclusivity (DE)? (Yes/ No) Is yes, please provide: a) DCA reference country (for DE) b) Date of approval in reference country c) Duration of DE granted in reference country d) Letter of intent
17	Is this product certified halal? (Yes/ No) If yes, please provide: a) Halal certificate b) certificate number
18	Does this product contain a medical device component? (Yes/ No)

No.	Step I: Product Validation
19.	Is there any other manufacturer (repacker)? (Yes/ No) a) Manufacturer (repacker) name b) Manufacturer (repacker) address c) Certificate of Good Manufacturing Practice (GMP) d) Packaging Process
20.	Is this an imported product? (Yes/ No)

Step II:	
Part I: Administrative Data and Product Information	
No.	**Section A: Product Particulars**
1.	Active Ingredient
2.	Excipient
3.	Dosage Form
4.	Product Description
5.	Pharmacodynamics
6.	Pharmacokinetics
7.	Indication
8.	Recommended Dose
9.	Route of Administration
10.	Contraindication
11.	Warning and Precautions
12.	Interaction of Other Medicaments
13.	Pregnancy and Lactation
14.	Side Effects
15.	Symptoms and Treatment of Overdose
16.	Effects on Ability To Drive And Use Machine
17.	Preclinical Safety Data (*Not applicable for Generics*)
18.	Instructions for Use (e.g., incompatibilities - For injection only)
19.	Storage Condition
20.	Shelf Life

Step II:	
21.	Therapeutic Code/ ATC Code
	Section B: Product Formula
1.	Batch Manufacturing Formula
2.	Attachment of Batch Manufacturing Formula Documentation
	Section C: Particulars of Packing Please refer to **Appendix 23: Patient Dispensing Pack for Pharmaceutical Products**
1.	Pack Size (Fill details by weight/ volume/ quantity)
2.	Immediate Container Type (Container Type and Description) e.g. Aluminium/ Glass/ Metal/ Paper/ Plastic/ Others
3.	Barcode/ Serial No. (Optional)
4.	Recommended Distributor's Price (RM) (Optional)
5.	Recommended Retail's Price (RM) (Optional)
	Section D: Label (Mock-up) For Immediate Container, Outer Carton, Proposed Package Insert, Consumer Medication Information Leaflet (RiMUP) Please refer to: **Appendix 19: General Labelling Requirements** **Appendix 20: Specific Labelling Requirements**
1.	Proposed Label Mock-up for Immediate Container
2.	Proposed Label Mock-up for Outer Carton
3.	Proposed Package Insert
4.	Consumer Medication Information Leaflet (RiMUP)
5.	Label Mock-up for Diluent
	Section E: Supplementary Documentation
1.	Product Owner
2.	Letter of Authorization from Product Owner
3.	Letter of Appointment of Contract Manufacturer from Product Owner (if applicable)
4.	Letter of Acceptance from Contract Manufacturer (if applicable)

Step II:	
5.	Letter of Appointment of the Repacker from the Product Owner
6.	Letter of Acceptance from the Repacker
7.	Certificate of Pharmaceutical Product (CPP)
8.	CPP Issuing Body
9.	Is this product licensed to be placed on the market for use in the exporting country? (Yes/ No) (If no, please state the reason)
10.	Is the product on the market in the exporting country? (Yes/ No) (If no, please state the reason)
11.	Date of Issue of CPP
12.	Date of Expiry of CPP
13.	Certificate of Free Sale (CFS)
14.	CFS Issuing Body
15.	Date of Issue of CFS
16.	Date of Expiry of CFS
17.	Certificate of Good Manufacturing Practice (GMP)
18.	GMP Issuing Body
19.	Date of Issue of Certificate of GMP
20.	Date of Expiry of Certificate of GMP
21.	Is there any other manufacturer(s) involved? (Yes/ No) a) Manufacturer name b) Manufacturer address c) Processing Step d) Certificate of Good Manufacturing Practice (GMP)
22.	Importer (Name and address)
23.	Store (Name and address)
24.	Summary of Product Characteristics (Product Data Sheet)
25.	Company core Data Sheet (CCDS)
26.	Analysis Protocol
27.	Validation of Analysis Protocol
28.	Other Supporting Document (if any)

Step II:	
29.	Worldwide Registration Status
30.	Post-Approval Commitment(s)
31.	TSE Risk-Free Commitment
PART II: QUALITY OF PRODUCT	
	Section P: Drug Product (Finished Product)
	Section A: Quality Overall Summary
	Section B: Table of Contents
	Section C: Body of Data
1.	Description and Composition
2.	Pharmaceutical Development a) Information on Development Studies b) Components of the Drug Product c) Finished Products d) Manufacturing Process Development e) Container Closure System f) Microbiological Attributes g) Compatibility
3.	Manufacturer a) Batch Formula b) Manufacturing Process and Process Controls Manufacturing Process Flowchart c) Control of Critical Steps & Intermediates d) Process Validation and/or Evaluation
4.	Control of Excipients a) Specifications b) Analytical Protocol c) Validation of Analytical Protocol d) Justification of Specifications e) Excipient of Human or Animal Origin f) Novel Excipients
5.	Control of Finished Products a) Specifications b) Analytical Protocol c) Validation of Analytical Protocol d) Batch Analyses Certificate of Analysis (CoA) – 2 batches

Step II:	
	e) Characterization of impurities f) Justification of Specifications g) Viral Inactivation/Removal Studies (applicable to biologics) h) Plasma Master File (PMF) (applicable to biologics) i) Certificate of Fitness for Purpose/ Compliance Certificate/ Plasma Quality/ Certificate (applicable to biologics) j) Batch Release Certificates (2 batches) (applicable to biologics) k) Summary Lot Protocol (2 batches) (applicable to biologics)
6.	Reference Standards or Materials
7.	Container Closure System
8.	Stability
9.	Product Interchangeability/ Equivalent Evidence (Bioavailability/ Bioequivalence, BA/BE) Please refer to **Appendix 16: Bioequivalence (BE) Requirements**
No.	**Section S: Drug Substance** *Refer to **Appendix 11: Regulatory Control of Active Pharmaceuticals Ingredients (APIs)**
1.	General Information a) Nomenclature b) Structure and Attachment for Structure of Drug Substance c) General Properties
2.	Manufacturer a) Manufacturer Name and Address b) Description of Manufacturing Process and Process Controls c) Controls of Materials d) Controls of Critical Steps and Intermediates e) Process Validation and/or Evaluation f) Manufacturing Process Development
3.	Characterisation a) Elucidation of Structure and Characteristics b) Impurities
4.	Control of Drug Substances a) Specifications b) Analytical Procedures c) Validation of Analytical Procedures d) Batch Analysis e) Justification of Specifications
5.	Reference Standards or Materials

Step II:	
6.	Container Closure System
7.	Stability
PART III: NONCLINICAL DOCUMENT	
	Section A: Table of Contents
	Section B: Nonclinical Overview
1.	Overview of the Nonclinical Testing Strategy
2.	Pharmacology
3.	Pharmacokinetics
4.	Toxicology
5.	Integrated Overview & Conclusions
6.	List of Literature Citations
	Section C: Nonclinical Written and Tabulated Summaries
	Section D: Nonclinical Study Reports
	Section E: List of Key Literature References

PART IV: CLINICAL DOCUMENT	
	Section A: Table of Contents
	Section B: Clinical Overview
1.	Product Development Rationale
2.	Overview of Biopharmaceutics
3.	Overview of Clinical Pharmacology
4.	Overview of Efficacy
5.	Overview of Safety
6.	Benefits & Risks Conclusions
	Section C: Clinical Summary
1.	Summary of Biopharmaceutics Studies and Associated Analytical Methods
2.	Summary of Clinical Pharmacology Studies
3.	Summary of Clinical Efficacy
4.	Summary of Clinical Safety
5.	Synopses of Individual Studies

	Section D: Tabular Listing of all Clinical Studies
	Section E: Clinical Study Reports
	Section F: **List of Key Literature References, Published Clinical Papers, Latest Periodic Benefit-Risk Evaluation Report (PBRER) and Risk of Management Plan (RMP)**
PART IV: CLINICAL DOCUMENT	
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	Section B: Clinical Overview
1.	Product Development Rationale
2.	Overview of Biopharmaceutics
3.	Overview of Clinical Pharmacology
4.	Overview of Efficacy
5.	Overview of Safety
6.	Benefits & Risks Conclusions
	Section C: Clinical Summary
1.	Summary of Biopharmaceutics Studies and Associated Analytical Methods
2.	Summary of Clinical Pharmacology Studies
3.	Summary of Clinical Efficacy
4.	Summary of Clinical Safety
5.	Synopses of Individual Studies
	Section D: Tabular Listing of all Clinical Studies
	Section E: Clinical Study Reports
	Section F: **List of Key Literature References, Published Clinical Papers, Latest Periodic Benefit-Risk Evaluation Report (PBRER) and Risk of Management Plan (RMP)**
PART IV: CLINICAL DOCUMENT	
	Section A: Table of Contents
	Section B: Clinical Overview
1.	Product Development Rationale
2.	Overview of Biopharmaceutics
3.	Overview of Clinical Pharmacology

4.	Overview of Efficacy
5.	Overview of Safety
6.	Benefits & Risks Conclusions
	Section C: Clinical Summary
1.	Summary of Biopharmaceutics Studies and Associated Analytical Methods
2.	Summary of Clinical Pharmacology Studies
3.	Summary of Clinical Efficacy
4.	Summary of Clinical Safety
5.	Synopses of Individual Studies
	Section D: Tabular Listing of all Clinical Studies
	Section E: Clinical Study Reports
	Section F: **List of Key Literature References, Published Clinical Papers, Latest Periodic Benefit-Risk Evaluation Report (PBRER) and Risk of Management Plan (RMP)**

2. ABRIDGED EVALUATION

No.	Product Category
1.	* Generics (Non-Scheduled Poison)
2.	Health Supplements: a) General or Nutritional Claims b) Functional Claims (Medium)
3.	Natural Products

* Generics (non-scheduled poison) that are evaluated under abridged evaluation include, but are not limited, to the following:

a) Antiseptics/ skin disinfectants;
b) Locally-acting lozenges/ pastilles;
c) Topical analgesic/ counter-irritants;
d) Topical nasal decongestants;
e) Emollient/ demulcent/ skin protectants;
f) Keratolytics;
g) Anti-dandruff;
h) Oral care;
i) Anti-acne;
j) Medicated plasters/ patch/ pad; and
k) Topical antibacterial.

2.1 General Requirements for Abridged Evaluation

No.	Step I: Product Validation
1.	Product Name Please provide brand name and full product name
2.	Dosage Form
3.	Active Ingredient(s) a) Active Ingredient name b) Strength of Active Ingredient (Quantity unit per dose) c) Source of Active Ingredient (Animal – e.g. Bovine, Porcine, Ovine or Others/ Plant/ Others) d) Form of Active Ingredient e) Remarks (if any)
4.	Excipient(s) a) Excipient name b) Strength of Excipient (Quantity unit per dose) c) Function of excipient (e.g. absorbent, diluents, bulking agent, coating agent, anti-caking agent etc.) d) Source of excipient e) Remarks (if any)
5.	Is there any source of ingredients derived from animal origin, including active ingredient? (Yes/ No) If yes, please declare the origin
6.	Manufacturer (Name and Address)
7.	Is there any contract manufacturer involved? (Yes/ No)
8.	Is the product a second source product? (Yes/ No) If yes, please provide: a) Letter of declaration stating that this product is a second source product b) Registration number and product name of the first source
9.	Is there any repacker/ packer involved? (Yes/No)
10.	Is the product manufactured for export only? (Yes/No)
11.	Is this an imported product? (Yes/ No)
12.	Does this product containing any premix? (Yes/ No) a) State your premix form b) Manufacturer name c) Manufacturer address d) Certificate of Good Manufacturing Practice (GMP) e) Formulation f) Manufacturing Process g) Specification of Analysis

No.	Step I: Product Validation
	h) Certificate of Analysis (CoA)
13.	Is this a replacement product? (Yes/ No) If yes, please provide: a) Letter of Declaration stating that this product is a replacement product b) Registration number and product name of the replaced product
14.	Is this product certified halal? (Yes/ No) If yes, please provide: a) Halal certificate b) certificate number

Step II:	
No.	**Section A: Product Particulars**
1.	Active Ingredient
2.	Excipients
3.	Dosage Form
	a) Source of Capsule Shell
	b) Certificate to verify the source of the capsule shell
	c) Coloring agent used in capsule shell (Please attach CoA of the capsule shell)
4.	Product Description
5.	Indication
6.	Recommended Dose
7.	Route of Administration
8.	Contraindication
9.	Warning and Precautions
10.	Interaction of Other Medicaments
11.	Pregnancy and Lactation
12.	Side Effects
13.	Symptoms and Treatment of Overdose
14.	Effects on Ability To Drive And Use Machine
15.	Preclinical Safety Data
16.	Instructions for Use

Step II:	
17.	Storage Condition
18.	Shelf Life
19.	Therapeutic Code/ ATC Code
No.	**Section B: Product Formula**
1.	Batch Size
2.	Batch Manufacturing Formula
3.	Attachment of Batch Manufacturing Formula Documentation
No.	**Section C: Particulars of Packing** Please refer to **Appendix 23: Patient Dispensing Pack for Pharmaceutical Products**
1.	Pack Size (Fill details by weight/ volume/ quantity) Measurement Type
2.	Immediate Container Type (Container Type and Description) e.g. Aluminum/ Glass/ Metal/ Paper/ Plastic/ Others
3.	Barcode/ Serial No. (Optional)
4.	Recommended Distributor's Price (RM) (Optional)
5.	Recommended Retail's Price (RM) (Optional)
6.	Other Related Attachment (if any)
No.	**Section D: Label (Mock-up) For Immediate Container, Outer Carton, Proposed Package Insert, Consumer Medication Information Leaflet (RiMUP)** Please refer to: **Appendix 19: General Labelling Requirements** **Appendix 20: Specific Labelling Requirements**
1.	Proposed Label Mock-up for Immediate Container
2.	Proposed Label Mock-up for Outer Carton
3.	Proposed Package Insert
4.	Proposed Patient Information Leaflet (PIL) / Consumer Medication Information Leaflet (RiMUP)
No.	**Section E: Particulars of Product Owner, Manufacturer, Importer and Other Manufacturer(s) Involved and Store address**
1.	Product Owner

Step II:	
2.	Letter of Authorization from Product Owner
3.	Letter of Appointment of Contract Manufacturer from Product Owner (if applicable)
4.	Letter of Acceptance from Contract Manufacturer (if applicable)
5.	Letter of Appointment of the Repacker from the Product Owner
6.	Letter of Acceptance from the Repacker
7.	Certificate of Pharmaceutical Product (CPP)
8.	CPP Issuing Body
9.	Is this product licensed to be placed on the market for use in the exporting country? (Yes/ No) (If no, please state the reason)
10.	Is the product on the market in the exporting country? (Yes/ No) (If no, please state the reason)
11.	Date of Issue of CPP
12.	Date of Expiry of CPP
13.	Certificate of Free Sale (CFS)
14.	CFS Issuing Body
15.	Date of Issue of CFS
16.	Date of Expiry of CFS
17.	Certificate of Good Manufacturing Practice (GMP)
18.	GMP Issuing Body
19.	Date of Issue of Certificate of GMP
20.	Date of Expiry of Certificate of GMP
21.	Is there any other manufacturer(s) involved? (Yes/ No) a) Manufacturer name b) Manufacturer address c) Processing Step d) Certificate of Good Manufacturing Practice (GMP)
22.	Importer (Name and address)
23.	Store (Name and address)
24.	***Analysis Protocol***
25.	***Validation of Analysis Protocol ***

Step II:	
26.	Other Supporting Document (if any)
27,	Post-Approval Commitment(s)
28.	TSE Risk-Free Commitment
PART II: QUALITY OF PRODUCT	
No.	**Section P: Drug Product (Finished Product)**
1.	Control of Finished Products a) Specifications b) Analytical procedures c) Validation of Analytical Procedures d) Batch Analyses - Certificates of Analysis (CoA) e) Manufacturing Process and Process Control f) Control of Critical Steps and Intermediate
2.	Stability
No.	**Section S: Drug Substance**
1.	Control of Drug Substances a) Specifications b) Certificates of Analysis (CoA)

APPENDIX 16

BIOEQUIVALENCE (BE) REQUIREMENTS

1. BIOEQUIVALENCE (BE) REQUIREMENTS

1.1 Overview

In applications for generic medicinal products, the concept of bioequivalence is fundamental. The purpose of establishing bioequivalence is to demonstrate equivalence in biopharmaceutics quality between the generic medicinal product and a comparator medicinal product in order to allow bridging of preclinical tests and of clinical trials associated with the comparator medicinal product. A generic medicinal product is a product which has the same qualitative and quantitative composition in active substances and the same dosage form as the medicinal product, and whose bioequivalence with the comparator medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy.

Applicants are advised to refer to and be familiar with the latest ASEAN Guideline for The Conduct of Bioequivalence Studies regarding the recommendation for establishing the interchangeability of generic product with comparator product. In addition, other relevant and latest international guidelines, e.g. by EMA, USFDA, ICH should also be referred to complement the ASEAN Guideline. These guidelines are to be read in conjunction with pertinent directives, circulars and updates regarding implementation of bioequivalence requirements in Malaysia, which will be updated periodically on the *NPRA website*.

1.2. Scope of Implementation

Bioequivalence (BE) requirement is implemented by stages for generic product applications in Malaysia.

Currently, this requirement is applicable to all generic products in the form of oral solid dosage forms with systemic actions. The following **Table 1** summarizes types of dosage forms that are required to submit BE data for new application of generic product registration or product registration renewal. The scope of implementation is not exhaustive and will be reviewed accordingly from time to time upon scientific judgement and patient risk assessment by the National Drug Authority. As for now, dosage forms that are not covered within the scope are not required to submit BE data during product registration or product registration renewal.

Table 1: Implementation of BE Requirement

Types of dosage form	Directives
All generic products containing scheduled poison in the form of **modified release**, oral, solid dosage form.	*Keperluan Akreditasi Pusat Kajian Bioavailability/ Bioekuivalens Bagi Produk Dalam Bentuk* Modified Release, *Bil. (3) dlm. BPFK/ PPP/01/03 Jld.3* (12 June 2013)
All generic products containing scheduled poison in the form of **immediate release**, oral, solid dosage form.	Directive No. 1, 2011: *Direktif Penguatkuasaan Keperluan Kajian Bioekuivalens bagi Semua Produk Generik* 'Immediate Release, Oral, Solid Dosage Form' *yang Mengandungi Bahan Aktif Racun Berjadual Serta Akreditasi Pusat Kajian Bioekuivalens*, *Bil. (10) dlm. BPFK/PPP/01/03 Jld.1* (2 March 2011)
Bioequivalence study report for all registered generic products containing scheduled poison with **effervescent, dispersible, orodispersible, sublingual, buccal and chewable** dosage forms	(i) Directive No, 3, 2015*: Direktif Penguatkuasaan Keperluan Kajian Bioekuivalens (BE) Bagi Semua Produk Generik Dalam Bentuk Dos Oral Tablet/Kapsul Yang Bersifat* Effervescent, Dispersible, Orodispersible, Sublingual, Buccal *dan* Chewable *Yang Mengandungi Bahan Aktif Racun Berjadual*, *Bil. (27) dlm. BPFK/PPP/07/25* (23 February 2015) (ii) *Lanjutan Tarikh Penguatkuasaan Untuk Memenuhi Keperluan Kajian Bioekuivalens* (BE) *bagi Produk Generik dalam Bentuk Dos Oral Tablet/Kapsul yang Bersifat* Effervescent, Dispersible, Orodispersible, Sublingual, Buccal *dan* Chewable *yang Mengandungi Bahan Aktif Racun Berjadual*, *Bil. (45) dlm. BPFK/PPP/01/03 Jld.3* (31 May 2016)

Should further clarification be needed on the BE requirements, kindly contact **be_sug@npra.gov.my**

1.3 Documentation of BE Study Report

A complete BE report with all the appendices and comparative dissolution profile data/report according to the relevant guidelines shall be submitted during generic product registration application. The complete BE report should consist of BE study protocol, clinical study report, method validation report, bioanalytical report and pharmacokinetic & statistical report. Applicants are advised to refer to the *Bioequivalence Study Report Submission Checklist* in preparation of dossier for submission. The complete documentation should be submitted in QUEST3+ system under section P9 Product Interchangeability/ Equivalence Evidence. Hardcopy of the report shall be requested when deemed necessary.

1.4 Bioequivalence (BE) Study Centre Accreditation

As of 1 January 2012, all BE studies intended to be used to support product registration review by the NPRA must be conducted at clinical and bioanalytical facilities that are listed under the NPRA BE Centre Compliance Programme. The list of accredited facilities is available on the *NPRA website*.

For BE studies that were conducted outside the period of facility listing on the NPRA BE Centre Compliance Programme; or were conducted at facilities not listed on the Programme, the applicant may apply for the "*Evaluation on the Need for BE Study Inspection*" to the Centre of Compliance & Quality Control (PKKK). Successful applications would allow the BE studies to be accepted for product registration review. If the applications were not successful, a study specific inspection would be required. The application form, additional details and procedure on how to apply for the *"Evaluation on the Need for BE Study Inspection"* and study specific inspections can be obtained from the *NPRA website*.

Applicable directives and circulars regarding the requirements above are as below:

Direktif Penguatkuasaan Keperluan Kajian Bioekuivalens Bagi Semua Produk Generik 'Immediate Release, Oral, Solid Dosage Form' *yang Mengandungi Bahan Aktif Racun Berjadual Serta Akreditasi Pusat Kajian Bioekuivalens* *Bil. (10) dlm. BPFK/PPP/01/03 Jld.1* (2 March 2011)
Makluman susulan berkaitan BE *Bil. (6)dlm. BPFK/PPP/01/03 Jld. 3* (12 September 2013)
Direktif Penguatkuasaan Keperluan Kajian Bioekuivalens (BE) Bagi Produk Generik Dalam Bentuk Dos Oral Tablet/ Kapsul Yang Bersifat Effervescent, Dispersible, Orodispersible, Sublingual, Buccal *dan* Chewable *Yang Mengandungi Bahan Aktif Racun Berjadual* *Bil. (27)dlm. BPFK/PPP/07/25* (23 February 2015)
Malaysian Guideline for Bioequivalence Inspection (First Edition)
Direktif Pelaksanaan Penilaian Keperluan Pemeriksaan Kajian Bioekuivalens (BE) *NPRA.600-1/9/13 (3)* (21 July 2020)

2. Investigational Products

2.1 Test Product

The test product used in the BE study should be manufactured at the same drug product manufacturing site by the same manufacturing process and manufactured with the same drug substance and formula as the generic product proposed for registration in Malaysia. The batch size of test product used in the BE study should also be at least 100,000 units or 1/10 of production scale, whichever is greater, unless otherwise justified. Any deviation from this requirement should be justified with additional documentation to ensure the sameness of both test product and product proposed for registration. Applicants are advised to refer to FAQ on the NPRA website for the additional documentation required.

2.2 Reference Product

The reference product used in the BE study must be the same as the innovator/ comparator products which have been registered with Drug Control Authority (DCA) in Malaysia. A generic product for which its innovator has never been registered in Malaysia will be classified under Hybrid application.

For purpose of product registration in Malaysia, applicants are advised to use Malaysia comparator product (MCP) to conduct the BE studies. The *list of Malaysia comparator product* is available on the NPRA website.

Applicant should provide a copy of the outer carton label which clearly showing batch number, manufacturer address, expiry date and the prescribing information (product leaflet) of the reference product used in the BE study for verification purposes.

Should the reference product use in the BE study was manufactured at a different site from the MCP, or manufacturer address was not stated on the outer carton, the applicant should justify and prove that the BE reference product is identical with the MCP in the following aspects:-

(i) The ingredients in the BE reference product are qualitatively identical to the Malaysia comparator product except minor differences in excipient (e.g. colouring and ink) that will not affect bioavailability of the reference product.

(ii) Comparative dissolution profile of the BE reference product is similar with the Malaysia comparator product. The CDP should be conducted as per requirement in Appendix I of ASEAN Guideline for the Conduct of Bioequivalence Study. It is highly recommended to conduct the CDP between reference product and MCP simultaneously to reduce potential variabilities and avoid comparison and compilation of historical data.

(iii) The drug substance does not have a narrow therapeutic index

Should the MCP be no longer available or could not be found on the list of comparators, kindly contact **be_sug@npra.gov.my** for further assistance.

3. Study Design

3.1 Immediate Release Product

For products where the Summary of Product Characteristic (SmPC) recommends intake of the comparator medicinal product on an empty stomach or irrespective of food intake, the BE study should be conducted under fasting conditions. BE study should be conducted under fasting conditions as this is considered to be the most sensitive condition to detect a potential difference between formulations. For products where the SmPC recommends intake of the comparator medicinal product only in fed state, the BE study should generally be conducted under fed conditions.

3.2 Modified Release Product

Single dose BE studies under both fasting and fed conditions should be submitted. Multiple dose study in fasting or fed state will be requested when deemed necessary.

4. Dissolution Testing and Similarity of Dissolution Profile

4.1 General Aspects of Dissolution Testing as Related to Bioavailability

During the development of a medicinal product, a dissolution test is used as a tool to identify formulation factors that are influencing and may have a crucial effect on the bioavailability of the drug. As soon as the composition and the manufacturing process are defined, a dissolution test is used in the quality control of scale-up and of production batches to ensure both batch-to-batch consistency and that the dissolution profiles remain similar to those of pivotal clinical trial batches. Furthermore, in certain instances a dissolution test can be used to waive a BE study. Therefore, dissolution studies can serve several purposes:

(i) Testing on product quality

- To get information on the test batches used in bioequivalence studies and pivotal clinical studies to support specifications for quality control
- To be used as a tool in quality control to demonstrate consistency in manufacture
- To get information on the reference product used in bioavailability/bioequivalence studies and pivotal clinical studies

(ii) Bioequivalence surrogate inference

- To demonstrate in certain cases similarity between different formulations of an active substance and the reference medicinal product (biowaivers e.g., variations, formulation changes during development and generic medicinal products)
- To investigate batch-to-batch consistency of the products (test and reference) to be used as basis for the selection of appropriate batches for the in-vivo study

4.2 Comparative Dissolution Profile (CDP)

In order to compare the dissolution profile of the products, the dissolution data should be generated under the same test conditions, if possible, on the same day. It is highly recommended to conduct the dissolution testing concurrently to reduce potential variabilities and avoid comparison and compilation of historical data

4.2.1 Usual Testing Conditions

(i) Media buffer

The in vitro dissolution test should be conducted at three different buffers (normally pH1.2, 4.5, 6.8) and the media intended for product release (QC media, if applicable and available).

Surfactants should be avoided in comparative dissolution testing.

A statement that the API is not soluble in any of the media is not sufficient, and profiles in the absence of surfactant should be provided. The rationale for the choice and concentration of surfactant should be provided. The concentration of the surfactant should be such that the discriminatory power of the test will not be compromised.

(ii) Number of products to be tested

At least 12-unit of each investigative products should be used in CDP testing to enable statistical evaluation. The products should originate from batch of at least 1/10 of production scale or 100,000 units, whichever is greater, unless otherwise justified.

(iii) Agitation

Selection of speed of agitation should be properly justified. Stirrer used in paddle apparatus is usually at 50rpm for tablets and basket apparatus at 100rpm for capsules.

(iv) Sampling time points

Sampling time points should be sufficient to obtain meaningful dissolution profiles, and at least every 15 minutes. More frequent sampling during the period of greatest change in the dissolution profile is recommended. For rapidly dissolving products, where complete dissolution is within 30 minutes, generation of an adequate profile by sampling at 5- or 10-minute intervals may be necessary.

(v) Statistical comparison

Dissolution similarity may be determined using suitable statistical procedure e.g the f_2 similarity factor as described in ASEAN guideline or other international guidelines.

(vi) Documentation

Complete documentation of in vitro dissolution experiments is required including a study protocol, batch information on batches, detailed experimental conditions, validation of experimental methods, individual and mean results and respective summary statistics.

5. Biowaiver considerations

Generic products should demonstrate the bioequivalence evidence by in-vivo equivalence testing. Nevertheless, exemption on the submission of an in-vivo BE study can be considered in certain circumstances for generic products of oral solid dosage forms. Applicants should provide adequate data and justifications for not submitting the in-vivo data.

5.1 Waiver of Additional Strength(s)

In generic drug product application consists of several strengths, it may be sufficient to establish bioequivalence at only one or two strengths, depending on the proportionality in composition between the different strengths and BE test products. If bioequivalence has been demonstrated at the strength(s) that are most sensitive to detect a potential difference between products, in-vivo BE studies for the other strengths may be waived provided that the following requirements are fulfilled: -

(a) the different strengths of the generic product are manufactured by the same manufacturing process,

(b) the qualitative composition of the different strengths is the same,

(c) the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule)

If there is some deviation from quantitatively proportional composition, condition (c) is still considered fulfilled if condition (i) and (ii) or (i) and (iii) below apply to the strength used in the bioequivalence study and the strength(s) for which a waiver is considered

(i) the amount of the active substance(s) is less than 5 % of the tablet core weight or the weight of the capsule content;
(ii) the amounts of the different core excipients or capsule content are the same for the concerned strengths and only the amount of active substance is changed;
(iii) the amount of a filler is changed to account for the change in amount of active substance. The amounts of other core excipients or capsule content should be the same for the concerned strengths

(d) appropriate comparative dissolution profile testing should confirm the adequacy of waiving additional in-vivo bioequivalence testing. Similarity of the dissolution profiles across the physiological pH range between additional strengths of the generic products and the strength of the generic product used in the BE study should be demonstrated. In addition, CDP testing demonstrating similar profiles at the same dose (e.g. two 10mg tablets versus one 20mg tablets) may be required.

If the data and justifications are considered not adequate, applicant will be required to provide relevant biopharmaceutics data, e.g. in-vivo BE study.

Applicants are advised to refer to the checklist "*Application For A Biowaiver: Additional Strength*" and submit relevant documents when requesting for biowaiver for additional strength.

5.2 BCS-based Biowaiver

The BCS (Biopharmaceutics Classification System)-based biowaiver approach is intended to reduce the need for in-vivo bioequivalence studies if an assumption of equivalence in in-vivo performance can be justified by satisfactory in vitro data. The BCS is a scientific approach based on the aqueous solubility and intestinal permeability characteristics of the drug substance(s). The BCS categorizes drug substances into one of four BCS classes as follows:

Class I : high solubility, high permeability

Class II : low solubility, high permeability

Class III: high solubility, low permeability

Class IV: low solubility, low permeability

5.2.1 Consideration for BCS-based Biowaiver Criteria

(i) BCS-based biowaivers are applicable for immediate-release oral solid dosage forms with systemic action.

(ii) For immediate release product in fixed dose combination, all the drug substances in the combination should meet the BCS-based biowaiver criteria.

(iii) Biowaiver may also be applicable if test and reference products contain different salts provided that both belong to BCS Class I (high solubility and high permeability).

(iv) Drug products with buccal or sublingual absorption are not eligible for a BCS-based biowaiver application

(v) Drug products having a narrow therapeutic index are excluded from consideration for a BCS-based biowaiver

(vi) Biowaiver is not applicable when the test product contains a different ester, ether, isomer, mixture of isomers, complex or derivative of a drug substance from that of the reference product, since these differences may lead to different bioavailabilities not deducible by means of experiments used in the BCS-based biowaiver concept.

Currently NPRA allows only BCS-based class 1 biowaiver application. Applicants are advised to prove that the generic product and drug substances are highly soluble and highly permeable with sufficient data and documentation as per requirement on the checklist *Application For Biopharmaceutics Classification System (BCS) Biowaiver*.

BCS-based class 1 application should be product specific and should not based on list of substance in the particular BCS class. If a generic product is to be marketed in several strength(s) and the submission is based on a BCS-based biowaiver approach, a complete set of documents is required for each strength, as it will be evaluated independently.

In situation where the applicant is unable to provide satisfactory documents to support BCS-based class 1 biowaiver application, biowaiver request may not be considered and BE study should be conducted.

5.3 Waiver for Second Source Product

In general, for a second source application of a generic product (immediate release, oral solid dosage form), BE study report from the actual manufacturing site must be submitted during the submission of application for registration. The base of this requirement is due to the difference in manufacturing site from the first source that may change the characteristic and specifications of a second source product.

However, biowaiver may be considered as a surrogate to in-vivo BE study for the second source product, provided that all the following conditions are fulfilled:

(a) BE study conducted using the registered first source product has been evaluated by NPRA and found satisfactory.

(b) Comparative Dissolution Profile (CPD) data between the second source product against the registered first source product is submitted

(c) The second source product is the same as registered first source product used in the BE study in terms of:

- Product formulation.
- Equipment used in the manufacturing process.
- Source and supplier of raw material.
- Quality control and specifications of raw material.
- Manufacturing process of product and standard operating procedures.
- Environmental conditions during the manufacturing process of product.
- Quality control and specifications of finished product.

(d) CDP must be conducted in accordance to ASEAN Guidelines for The Conduct of Bioequivalence Studies including the calculation of similarity factor (f2) to prove the similarity of these two products.

(e) Process validation has been conducted on three pilot or commercial batches of the second source product and found satisfactory by the NPRA.

This exemption is not applicable for any new submission of application for registration of a first source product. BE study must be conducted for this product which is manufactured at the actual manufacturing site submitted for registration.

Disclaimer: NPRA reserves the right to request for any additional information required for evaluation if deemed appropriate, to determine the product interchangeability of the generic product to the MCP.

6. References

a. ASEAN Guideline for the Conduct of Bioequivalence Studies

b. ICH M9 Guideline on Biopharmaceutics Classification System-based Biowaivers

c. Annex 6 WHO Technical Report Series 1003, 2017

APPENDIX 17

PRODUCT NAMES NOT PERMITTED TO BE REGISTERED

Note:

1. *This list is not meant to be exhaustive and is subject to review from time to time*
2. *The Authority reserves the right to disallow any other words or phrases for product names, which in its opinion is misleading, improper or not factual.*

No.	Non-Permissible Product Names	Examples
1.	**20 disease names as stated in the Medicines (Advertisement and Sale) Act 1956 (Revised 1983)**	Diabetes, Asthma, Cancer
2.	**Prohibited use of a single active ingredient as a product name in products containing more than one active ingredient, except if the product name contains words such as 'Plus, Compound, Complex, Herbanika'**	Tongkat Ali Capsule (if product contains tongkat ali, ginseng, etc.)
3.	**Use of superlatives** Names indicating superiority in efficacy	Power/ Kuasa, Superior, Pure, Mustajab, Safe, Healthy/ Sihat, Penawar/ Shifa, VIP, Good, Heal/ Sembuh, Premium, Mustajab, Men/ Women/ Children Complete, Men/ Women/ Children Enriched, Paradise/ Syurga, Menawan, Booster
4.	**Use of word spelling that may cause confusion** **Words involving names of/part thereof:** i) 20 disease names prohibited in the Medicines (Advertisement and Sale) Act 1956 (Revised 1983) ii) Diseases without scientific evidence of efficacy/ prescription medication to treat diseases/ parameters that indicate certain diseases (e.g. insulin, glucose) iii) Prohibited indication (e.g. to detoxify body)	a) Go Out = GOUT b) UTix = Urinary Tract Infection c) Diabecine = Diabetes d) Metformon = Metformin e) Insuprem = Insulin f) Glucosey = Glucose g) DetoxB = Detox body

No.	Non-Permissible Product Names	Examples
5.	**Use of names that may cause ambiguity**	B For Energy?
6.	**Use of names that may be offensive or indecent**	SENXBIG=SEnXBIG(label) Sexy, Enjoy, Paradise, Heavenly, Blue boy, Casanova, Desire *(Dezire),Sensual (Xenxual),Asmara,Syok*
7.	**Use of product names incoherent with the approved indication** The name contains only one product claim, but the product has more than one approved indication	Cough Syrup X= Approved indication for cough, dizziness, flu and itch
8.	**Use of product names with elements of ludicrous belief** Statements referring to ancient beliefs/ negative spirits/ supernatural power	Words such as miracle, magic, magical, miraculous, saintly, heavenly
9.	**Use of product names similar to existing approved product names** Product names similar to the spelling and pronunciation of words of existing product names	Tenormin vs Tenormine vs Tenormy Re-Liv vs Re-Lif
10.	**Use of product names that may cause ambiguity in the nature of the product (drug/ food/ beverage)** Product names similar to a food/ beverage product	Juice, Health drink, Beverage, Kooky
11.	**Use of product names representing professional advice or opinion or the profession**	Dr Sunny, Dr Noortier Rooibose Tea, Professor, Herbalist, Doctor
12.	**Use of product names representing weight loss/ slimming properties/ names that can be associated with weight loss/ slim**	Slim, Langsing, Trim, Trimnfit, *Sleen, Kurus, Susut perut, Xlim, Weight watcher*

No.	Non-Permissible Product Names	Examples
13.	**Use of product names referring to any religious content**	Maksum, Mahmudah, Arifbillah
14.	**Use of product names referring to internal organs**	Leever, Brainey, Kidnee, etc.
15.	**Use of abbreviation as a product name, except if it carries no meaning**	TB, UTI, HB, etc.
16.	**Use of product names deemed to be unbefitting (e.g. traditional, non-professional) for pharmaceutical products**	Cap Ikan Emas, Brand Ayam Jati, Tablet Kuat Badan
17.	**Other prohibited product names**	Minda, IQ, Smart, Genius, Ultra Mega, Detox

APPENDIX 18

LIST OF PERMITTED, PROHIBITED AND RESTRICTED SUBSTANCES

IMPORTANT NOTE:

The following lists are by no means exhaustive.

Contents:

1. List of Prohibited and Restricted Active Ingredients and Combination

1.1 List of Prohibited Active Ingredients and Combinations

a) Specific Active Ingredients

b) Combinations

1.2 List of Restricted Active Ingredients and Combinations

a) Specific Active Ingredients

b) Combinations

2. List of Prohibited and Restricted Excipients

2.1 List of Prohibited Excipients

2.2 List of Restricted Excipients

3. List of Permitted and Restricted Colouring Agents

3.1 List of Permitted Colouring Agents

3.2 List of Restricted Colouring Agents

1. LIST OF PROHIBITED AND RESTRICTED ACTIVE INGREDIENTS AND COMBINATION

1.1 List of Prohibited Active Ingredients and Combinations

a) Prohibited Active Ingredients

NO.	PROHIBITED ACTIVE INGREDIENTS
1.	1,3-dimethylamylamine (DMAA)
2.	Aristolochic Acid
3.	Aminopyrine/ Amidopyrine
4.	Astemizole
5.	Bacillus Coagulans
6.	Berberine
7.	Butobarbitone
8.	Chlormezanone
9.	Cisapride
10.	Conjugated Linoleic Acid
11.	Crinis Carbonisatus
12.	Danthron
13.	Dipyrone
14.	Enterococcus Faecalis
15.	Enterococcus Faecium
16.	Ethenzamide
17.	Euflavine
18.	Furazolidone
19.	Fenfluramine/ Dexfenfluramine
20.	Gadodiamide
21.	Gentian Violet

NO.	PROHIBITED ACTIVE INGREDIENTS
22.	Gamma-Butyrolactone (GBL)
23.	Gamma-Aminobutyric Acid (GABA)
24.	Gamma-Hydroxybutyric Acid (GHB)
25.	Haloquinol
26.	Hexachlorophene
27.	Mercurochrome
28.	Nimesulide
29.	Novobiocin
30.	Oxyphenisatin Acetate/ Acetophenolisatin
31.	Oxyphenbutazone
32.	Pergolide
33.	Phenacetin
34.	Phenazone/ Antipyrine - Propylphenazone - Isopropylphenazone
35.	Phenylbutazone
36.	Phenylpropanolamine
37.	Piperazine
38.	Prenylamine
39.	Quinalbarbitone
40.	Salicylamide
41.	Sibutramine
42.	Stanozolol
43.	Sulphaguanide
44.	Thioridazine
45.	Tegaserod

NO.	PROHIBITED ACTIVE INGREDIENTS
46.	Terfenadine

b) <u>Prohibited Combinations</u>

NO.	PROHIBITED COMBINATIONS
1.	Ampicillin + Cloxacillin
2.	Antibiotics + Papain/ Prolase
3.	Antacid + Charcoal
4.	Combinations With Any Barbiturates
5.	Combinations of Two or More Analgesic with the Same Mode of Action
6.	Combinations Of Vitamin (S) With Other Drugs: a. Vitamin (S) + Appetite Suppressant b. Vitamin (S) + Corticosteroid *NOTE:* Combination of calcipotriol (Vitamin D3 analogue) + corticosteroid for topical treatment of psoriasis may be allowed, subject to provision of data to support efficacy and safety c. Vitamin (S) + Analgesic d. Vitamin (S) + Laxative e. Vitamin (S) + Slimming Agents
7.	Cough, Cold and Allergy Products Containing: a. Four or More Pharmacological Groups in One Product. b. Two or More Drugs from the Same Pharmacological Group c. Antypyretic - Analgesic + Expectorant d. Anticholinergic + Bronchodilator e. Codeine + Ephedrine/ Pseudoephedrine f. Methapyrilene g. Paracetamol + Mucolytic/ Expectorant
8.	Combinations Containing Antacid and Surface Local Anaesthetic Agent
9.	Combinations Containing Dextropropoxyphene

NO.	PROHIBITED COMBINATIONS
10.	Combinations Containing Spironolactone
11.	Corticosteroids + Antihistamines
12.	Eye Drops Containing Vitamin
13.	Gripe Water Containing Alcohol
14.	Propanolol + Hydralazine
15.	Propanolol + Spironolactone
16.	Topical Preparation Containing Combination of Antibiotic, Antifungal and Steroid

1.2 List of Restricted Active Ingredients and Combinations

Specific Active Ingredients	Not Allowed in the Specified Preparation(s) or Condition
1. Acetic Acid	Expectorant
2. Allantoin	Eye Drop
3. Allergen Extracts	Vaccines, Diagnostics
4. Amphetamine	Cough Mixtures, Appetite Suppressants
5. Animal Organ	All Preparations Except Natural Products
6. Antihistamine	Topical Use
7. Bismuth Salts Except Bismuth Subcitrate	Oral Preparations
8. Boric Acid/ Borax and Related Salts	Oral, Topical (Skin), Vaginal, Nasal Dosage Form
9. Buprenorphine	Single Active Ingredient Sublingual Tablet Formulation
10. Caffeine	All Preparations Except for an Oral Preparation in Combination with Paracetamol/ Acetaminophen or Combination with Ergotamine
11. Camphor	- Oral - External (>11%)
12. Chloroform	Expectorant
13. Codeine	Cough Syrup
14. Cocillana Liq. Extract	Expectorant
15. Cyproheptadine	Appetite Stimulant
16. Dextromethorphan	Single Active Ingredient in Tablet Form, including lozenges
17. Dihydrostreptomycin	Oral Antidiarrhoeals
18. Diphenoxylate	Liquid Oral Dosage For Anti-Diarrhoeal
19. Quinestrol, Oestrogen	Lactation Suppressant
20. Ethynodiol Diacetate	Oral Contraceptives
21. Euphorbia Liquid Extract	Expectorant
22. Gadopentetic acid	All except Intra-articular Formulation

Specific Active Ingredients	Not Allowed in the Specified Preparation(s) or Condition
23. Gatifloxacin	All Preparations Except for Eye Drop
24. Germanium	Non-Naturally Occurring
25. Hydroquinone	Oral
26. Lactobacillus Acidophillus	Antidiarrhoeal
27. Loperamide	Liquid Oral Dosage For Anti-Diarrhoeal
28. Lovastatin	In Red Yeast Rice: > 1 % w/w and > 10mg/Day
29. Lynooestrenol	Oral Contraceptives
30. L-Tryptophan	All Preparations Except Parenteral Nutrition Products And Enteral Feeding Products
31. Magnesium Ascorbryl Phosphate	Antipigmentation
32. Menthol	External Preparations >16%
33. Mestranol	Oral Contraceptives
34. Methylene Blue	Oral Preparations
35. Midazolam	All oral preparations, except 7.5mg coated tablet
36. Morphine	Cough Mixtures
37. Neomycin	Oral Antidiarrhoeal, Vaginal Tablets, Topical Powders, Aerosols, Nasal Preparations
38. Noradrenaline	Dental Preparations
39. Norgestrel	Oral Contraceptives
40. Paracetamol	Liquid Oral 500mg/5ml
41. Penicillin	Topical Use
42. Phenazopyridine	Urinary Analgesics
43. Phenolphthalein	Stimulant Purgative
44. Pizotifen	Appetite Suppressant
45. Podophyllum Resin	Oral Preparations
46. Pseudoephedrine	All Single Active Ingredient Formulations
47. Sulphonamides	Topical Use
48. Sulphur	All preparations Except External

Specific Active Ingredients	Not Allowed in the Specified Preparation(s) or Condition
	Preparation
49. Squill	Expectorant
50. Terpene Hydrate	Expectorant

Combinations	Not Allowed in the Specified Preparation(s)
1. Cough, Cold And Allergy Products Containing:	
i) Antimony Potassium Tartrate	Expectorant
ii) Allylisothiocyanate/ Mustard Oil	Nasal Decongestant
iii) Turpentine Oil	Expectorant/ Antitussive
2. Vitamin(s)	Eye Drops

2. LIST OF PROHIBITED AND RESTRICTED EXCIPIENTS

2.1 List of Prohibited Excipients	
1. Colouring Agents (Including in Capsule Shells)	**Amaranth (CI= 16185, FD & C Red No. 2, E123)**
2. Others	**Chlorofluorocarbons (CFC)**

2.2 List of Restricted Excipients	
Excipients	**Restrictions**
1. Colouring Agents (Including in Capsule Shells)	
a) Tartrazine (CI= 19140, FD & C Yellow No.5, E102)	Not allowed in the following preparations: – Oral; – Rectal; – Vaginal or – Nasal Preparations
b) Red 2G	Not allowed in the following preparations: – Oral Preparations; and – Preparations Used for Mucosa Membrane
2. Sweeteners/ Flavouring Agent	
a) Menthol	0 to 4mg/kg body weight/day (dosage and use in children should be clearly stated).
b) Saccharin and Salts	Limited to not more than 5mg/kg/day
c) Cyclamates	Limited to not more than 1.5mg/kg body weight/day
3. Preservatives	
a) Chloroform	Limited to not more than 0.5% in Pharmaceuticals for Internal Use

b) Thiomersal*	Not allowed in ophthalmic Preparations	
4. Others		
a) Phthalates	Variant	Maximum Limit of Daily Exposures (mg/kg body weight/day)
	Dibutyl Phthalate (DBP)	0.01mg/ kg/ day
	Diethyl Phthalate (DEP)	4mg/ kg/ day
	Polyvinyl Acetate Phthalate (PVAP)	2mg/ kg/ day
b) Cetrimide	Limited to less than 0.1% w/v (topical preparations for Natural Products)	

** For other preparations, the warning specified in **Appendix 20: Specific Labelling Requirements** shall be included in the package insert and product literature of products containing thiomersal.*

Additional Information

1. **Methylene Chloride/ Dichloromethane** are not allowed as solvent in film-coating for locally manufactured products.

   For details on implementation, refer to *Surat Pekeliling Berhubung Larangan Penggunaan 'Methylene Chloride' atau 'Dichloromethane (DCM)' Dalam Proses Pengilangan Produk Tempatan*: *Bil. (2)dlm.BPFK/30/06/2 Bhgn. 2* (23 May 2013)

2. **Alcohol** is not allowed except if it is essential to the formulation and no suitable alternatives to alcohol is available. The alcohol content shall be kept to the most minimum level as possible.

3. LIST OF PERMITTED AND RESTRICTED COLOURING AGENTS

3.1 List of Permitted Colouring Agents

NO.	COLOURING AGENTS	COLOUR INDEX NUMBER (CI)
1.	Allura Red AC/ FD & C Red No.40	16035
2.	Anthocyanins a. Those glycosides of 2-phenylbenzopyrylium salts which are anthocyanins b. The following anthocyanidin aglycones: i. Pelargonidin ii. Cyanidin iii. Peonidin iv. Delphinidin v. Petunidin vi. Malvidin	
3.	Black PN (Brilliant Black BN)	28440
4.	Brilliant Blue FCF	42090
5.	Calcium Carbonate	
6.	Carbo Medicinals/ Vegetalis; (Charcoal)	
7.	Caramel	
8.	Carmoisine (or Azorubine)	14720
9.	Carotenoids a. Alpha, Beta, Gamma-Carotene b. Bixin, Noribixin, Roucou c. Annatto d. Capsanthin, Capsorubin, (paprika extract) e. Lycopene f. Beta-Apo-8' carotenal (C 30) g. Ethyl ester of Beta-Apo-8 Carotenoic Acid (C30) i. Chlorophyll ii. Copper complexes of Chlorophyll and Chlorophyllins	 75120 40820 75810
10.	Chocolate Brown HT	20285
11.	Cochineal or Carminic Acid, Carmine from Cochineal	75470

NO.	COLOURING AGENTS	COLOUR INDEX NUMBER (CI)
12.	Curcumin	75300
13.	Fast Green FCF (FD & C Green No.3)	42053
14.	Green S (Acid Brilliant Green BS, Lissamine Green)	
15.	Indigo Carmine (Indigotine)	73015
16.	Lactoflavin, Riboflavin	
17.	Patent Blue V	42051
18.	Ponceau 4R (Cochineal Red A)	16255
19.	Quinoline Yellow	47005
20.	Xanthophylls a. Flavoxanthin b. Lutein c. Cryptoxanthin (Kryptoxanthin) d. Violoxanthin e. Rhodoxanthin f. Canthaxanthin	40850
21.	The Following Colouring Matters Natural to Edible Fruits or Vegetables: a. Alkannin b. Annatto (including eye) c. Carotene (including eye) d. Chlorophyll e. Flavine f. Indigo g. Osage h. Orange i. Persian Berry j. Safflower k. Saffron l. Sandalwood m. Turmeric n. or their pure coloring principles whether isolated from such natural colors or produced synthetically	75530
22.	Bole or Iron Oxide, Carbon Black (or Vegetable Origin), Titanium Dioxide	77891

NO.	COLOURING AGENTS	COLOUR INDEX NUMBER (CI)
23.	The Aluminium Salts (Lakes) of Any of the Scheduled Synthetic Dyes Approved for Use, (a) Alumina (Dried Aluminium Hydroxide)	
24.	Talc	
25.	Indigo Carmine/ FD & C Blue No. 2	73015
26.	Brilliant Blue FCF Ammonium Salt/ D & C Blue No. 4	42090
27.	Alizarin Cyanine Green F/ D & C Green No. 5	61570
28.	Toney Red/ D & C Red No. 17	26100
29.	Eosin YS Acid Form/ D & C Red No. 21	45380:2
30.	Eosinys Sodium Salt/ D & C Red No. 22	45380
31.	Phloxine B Acid Form/ D & C Red No. 27	45410:1
32.	Phloxine B Sodium Salt/ D & C Red No. 28	45410
33.	Helindone Pink CN/ D & C Red No. 30	73360
34.	Erythrosine/FD & C Red No. 3	45430
35.	Yellow 2G (Food Yellow)	
36.	Orange Yellow S Sunset Yellow FCF (FD & C Yellow No. 6, E110)	15985

3.2 List of Restricted Colouring Agents

The following colouring agents are **ALLOWED** in preparations as stated in the parentheses:

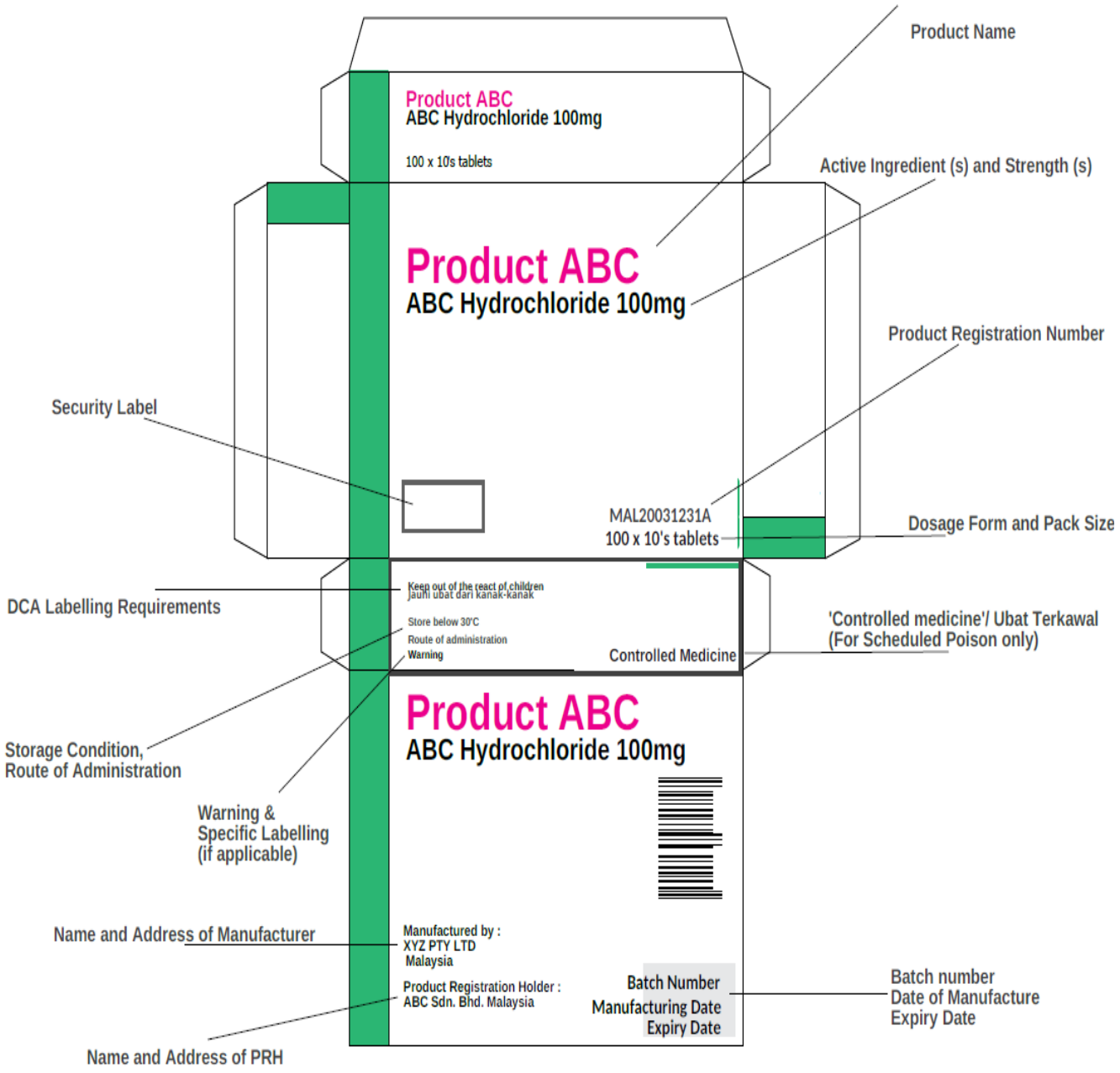
NO.	COLOURING AGENTS	COLOUR INDEX NUMBER (CI)
1.	Dihydroxyacetone (external use with specific drugs only)	
2.	Bismuth Oxychloride (external use only, including eye)	77163
3.	Ferric Ammonium Ferrocyanide (external use only, including eye)	
4.	Ferric Ferrocyanide (external eye only)	
5.	Chromium Hydroxide Green (external use only)	77289
6.	Chromium Oxide Green (external use only, including eye)	
7.	Guanine (external use only)	75170
8.	Prophyllite (external use only)	
9.	Mica (external use only, including eye)	77019
10.	Mica coated with titanium dioxide and/or iron oxide (internal use only) • for solid dosage form, not more than 3% of the preparation (in the case where the preparation was made using iron oxides, the preparation shall not contain more than 55% iron oxides)	
11.	Bronze (external use only, including eye)	
12.	Copper (external use only, including eye)	
13.	Zinc Oxide (external use only, including eye)	77947
14.	Quinizarine Green SS/ D & C Green No. 6 (external use only)	61565

NO.	COLOURING AGENTS	COLOUR INDEX NUMBER (CI)
15.	Pyranine Concentrated/ D & C Green No. 8 (external use only)	59040
16.	Orange II/ D & C Orange No. 4 (external use only)	15510
17.	Dibromofluorescein/ D & C Orange No. 5 (mouth wash, dentifrices, external use only)	45370
18.	Diiodofluorescein/ D & C Orange No. 10 (external use only)	45425
19.	D & C Orange No. 11 (external use only)	
20.	Ponceau SX/ FD & C Red No. 4 (external use only)	14700
21.	Lithol Rubin B/ D & C Red No. 6 (may be use in combination; total not more than 5mg/day)	15850
22.	Lithol Rubin B CA/ D & C Red No. 7 (may be used in combination; total not more than 5mg/day)	15850:1
23.	D & C Red No. 31 (external use only)	
24.	Deep Maroon/ D & C Red No. 34 (external use only)	15880:1
25.	D & C Red No. 39 (external use only, not more than 0.1%)	
26.	Uranine Acid Form/ D & C Yellow No. 7 (external use only)	45350:1
27.	EXT. D & C Yellow No. 7 (external use only)	
28.	Uranine Sodium Salt/ D & C Yellow No. 8 (external use only)	45350
29.	Tartrazine/ FD & C Yellow No. 5/MA Yellow A-2/ Aluminic Lake (external use only)	19140

APPENDIX 19

GENERAL LABELLING REQUIREMENTS

1. LABEL FOR IMMEDIATE CONTAINER AND OUTER CARTON



The following information in **Table 1** below shall be present on the label of a product at the outer carton, immediate container or blister/ strips:

No.	Parameters	Outer Carton (Unit Carton)	Immediate Labels	Blister/ Strips
1.	Product Name	✓	✓	✓
2.	Dosage Form	✓	✓*	NA
3.	Name of Active Substance(s)	✓	✓	✓**
4.	Strength of Active Substance(s)	✓	✓	✓**
5.	Batch Number	✓	✓	✓
6.	Manufacturing Date	✓	✓*	NA
7.	Expiry Date	✓	✓	✓
8.	Route of Administration	✓	✓	NA
9.	Storage Condition	✓	✓*	NA
10.	Country's Registration Number	✓	✓*	NA
11.	Name & Address of Product Registration Holder (PRH)	✓	✓*	Name/ Logo of Manufacturer/ Product Owner
12.	Name & Address of Manufacturer	✓ At least name of town/ city and country of manufacturer	✓* At least name of town/ city and country of manufacturer	NA
13.	Warnings and/or Specific Labelling (if applicable)	✓	✓*	NA
14.	Pack Sizes (unit/ volume)	✓	✓	NA
15.	Name & content of preservative(s) where present	✓	✓	NA
16.	Name & content of alcohol, where present	✓	✓	NA
17.	To declare source of ingredients derived from animal origin (active and excipient) including starting materials and gelatine	✓	✓	NA

No.	Parameters	Outer Carton (Unit Carton)	Immediate Labels	Blister/ Strips
18.	To declare the source of capsule shell (if applicable)	✓	✓	NA
19.	Recommended daily allowance (RDA) for vitamins/ multivitamins/ mineral preparations used as dietary supplements (optional)	✓	✓	NA
20.	The words "Keep medicine out of reach of children" or words bearing similar meaning in both *Bahasa Malaysia* & English	✓	✓*	NA
21.	Other country specific labelling requirements (if applicable)	✓	✓*	NA
22.	The words "Controlled Medicine" or "*Ubat Terkawal*" (For scheduled poison only)	✓	✓*	NA
23.	Security Label (Hologram)	✓ #	-	NA

NA: Not Applicable

* Exempted for small labels (i.e. 5ml and less) used for ampoules/ cartridge, vials, eye drops, ear drops, and nose drops.

** For multi-vitamins and minerals preparations, it is suggested to be labelled as "multi-vitamins and minerals".

\#
- i. If the product does not have an outer carton, the security label shall be affixed onto the immediate label.
- ii. For large volume parenteral (LVP) products defined as containers labelled as containing more than 100mL [based on the United States Pharmacopeia (USP)], the security label (hologram) shall be affixed on the immediate label of each unit of the product.
- iii. The security label (hologram), however, shall not be affixed to the outer shrink wrap of the product.

iv. The following are exempted from the security label requirement:

- Small labels (i.e. volume of 5mL and less). E.g. ampoules/ cartridges/ vials.
- Radiopharmaceutical with short half-life, temperature-sensitive and cold chain products. E.g. vaccines, etc.
- It is sufficient for the security label (hologram) to be affixed to the outer carton / unit of sale for small volume parenteral (SVP) products [defined as packaged in containers and labelled as containing 100mL or less based on the United States Pharmacopeia (USP)].

No. 15, 20, 22 and 23 of the above are country specific requirements for Malaysia.

Additional Requirements:

a) All labels and package inserts must be in *Bahasa Malaysia* or English. In addition to this, translation to another language is allowed.

b) If the product is without an outer carton, the inner label shall bear all the required information.

c) The link to the official company website or website for any purpose of product promotion by the PRH/ product owner/ manufacturer is not allowed to be printed on the product label (applicable to all product categories, including imported products). However, the company email address is permitted on the label.

d) The label colours shall differentiate the different strengths of the product as well as products containing different active ingredients that belong to the same PRH.

e) Only a single label artwork is permitted for all pack sizes of a registered product.

f) No stick-on label is permitted. Any usage of stick-on label shall have prior approval by the Authority. The label shall be made from good quality material and not easily torn or peeled off. The Authority will only consider the following situations:

Stick-on label of such information is permitted:

Words with "Controlled Medicine", "*Ubat Terkawal*", "Keep out of reach of children" and *"Jauhkan daripada capaian kanak-kanak"*, PRH information, and Malaysia Specific Labelling Requirements (if any) shall be printed in a single label.

g) The registration number shall be printed permanently on the product (inkjet) and it is not allowed to be printed on the stick-on label.

h) Use of QR code is permitted only for the purpose of monitoring inventory of the product, such as batch number, expiry date and manufacturing date, BUT NOT for linkage to any website. The addition of QR code on registered product labels without variation approval

from NPRA may be considered only if that is the only proposed change to the currently approved labels.

i) The label of a registered product containing any Scheduled Poison shall not have colourful artwork or graphics that can be misleading or will adversely influence caregivers'/patients'/children's perceptions of the appropriateness of the medication.

j) Font size of the product name on the label, including alphabets and numbers, shall be equal.

k) For a product containing two (2) or more active ingredients, the font of each active ingredient that is highlighted on the inner/outer carton must be of equal size and prominence.

- This does not refer to the product name, but the statement made on the label.
- Justification for highlighting only certain ingredients on the product name/label must be provided and is subject to approval by the Drug Evaluation Committee.

l) Declaration of nutrition information per serving (e.g. energy, carbohydrate, protein and fat) is not permitted on a health supplement product label.

2. PROHIBITED VISUAL/ GRAPHICS/ STATEMENTS ON LABEL

The list of prohibited visual/ graphics/ statements on label are as specified in **Appendix 19A: Prohibited Visual/ Graphics/ Statements On Label**.

Also refer to:

- **Appendix 6: Guideline on Registration of Health Supplements**
  Table 7: Prohibited Visual/ Graphics on Label
- **Appendix 7: Guideline on Registration of Natural Products**
  Table 11: Prohibited Visual/ Graphics/ Statement on Packaging Materials (Label, Box, Package Insert or Consumer Medication Information Leaflet)

APPENDIX 19A

PROHIBITED VISUAL/ GRAPHICS/ STATEMENTS ON LABEL

Notes:

1. *This list is not meant to be exhaustive and is subject to review from time to time.*
2. *The Authority reserves the right to disallow any other words, phrases or graphics for product label, which in its opinion is misleading, improper or not factual.*

No.	Issue	Example	Note
1.	Marketing strategy	"Money back guarantee" "Buy 1 free 1" "Backed by RM5 million product Liability Insurance"	-
2.	Usage guide promoting use of other product(s)	"After consumption of this product (Product A), it is recommended to take Product B for better results."	-
3.	Consumer testimonial	-	-
4.	Clinical trial results or any information on clinical trial done on product	"Clinically Tested" "Randomized Double Blind Placebo Control Clinical Study"	-
5.	Reference to Hadith/ Al-Quran/ Bible/ Religious books	-	-

No.	Issue	Example	Note
6.	Opinion of prominent figure(s) on the product or its active ingredient/ content	Opinion of product/formulation inventor	-
7.	Label design (graphic and colour) similar to labels from another company	-	-
8.	Statement on the active ingredient origin	Sourced from the Mountains of Alps	Allowed if proven true
9.	Introduction of founder/ manufacturer	-	-
10.	Logo with certification	SIRIM/ ISO / GMP/ HACCP	Prohibited on product label because certification renewal is on a yearly basis
11.	Name/ statement/ logo/ registered trademark that does not satisfy the specifications	"Dr. ABC's Formula" "Nothing like it"	-
12.	Special technique used/ superiority in ingredients	Capsule coat	Allowed if proven true
13.	Nutritional claims with analysis certificate attached	Calorie, Fat, Protein and others	-

No.	Issue	Example	Note
14.	Graphics or picture of internal organs	Kidney, Heart, Nerves.	-
15.	Gender symbol (male or female)	(♀ and/or ♂)	-
16.	Indecent photographs/ pornography/ graphics/ images	-	-
17.	Graphics incoherent with the indication	- Indicated for constipation, but the label depicts a slim lady, implying indication for weight loss. - Indicated for urination, but the label shows a water hose.	-
18.	Highlighting unnecessary body parts	Indicated for general health, but the label highlights male and female sexual organ parts	-
19.	Graphics of plants or animal that may cause confusion	Radix Ginseng improvised as a male sexual part	-
20.	Negative statements/ visual	- This product is GMO/ LMO free - This product is free from animal origin - Free from Preservative	-
21.	Other statements deemed relevant to be prohibited by the authority	This product is blended with premium quality	-

APPENDIX 20

SPECIFIC LABELLING REQUIREMENTS

NO.	SUBSTANCES
1.	5-ALPHA REDUCTASE INHIBITOR (5-ARI)
2.	ABIRATERONE
3.	ACE INHIBITORS
4.	ACETAZOLAMIDE
5.	ACETYLCYSTEINE
6.	ACETYLSALICYLIC ACID (ASPIRIN)
7.	ACTIVATED CHARCOAL/ ATTAPULGITE
8.	ALBENDAZOLE & BENZIMIDAZOLE ANTIHELMINTICS
9.	ALFALFA (*MEDICAGO SATIVA*)
10.	ALLOPURINOL
11.	AMBROXOL
12.	AMIODARONE
13.	AMOXICILLIN
14.	ANASTROZOLE
15.	ANTIDEPRESSANTS
16.	ANTIEPILEPTICS
17.	ANTIPSYCHOTIC AGENTS
18.	ARGININE
19.	ARIPIPRAZOLE
20.	ASPARTAME
21.	ATORVASTATIN

22.	AZITHROMYCIN
23.	BEE POLLEN
24.	BENZODIAZEPINE
25.	BENZOYL PEROXIDE
26.	BENZYL ALCOHOL
27.	BERBERINE ALKALOIDS – NATURAL OCCURING BERBERINE E.G. HYDRASTIS CANADENSIS (GOLDENSEAL), COPTIS CHINENSIS (COPTIS OR GOLDENTHREAD), FIBRAUREA CHLOROLEUCA ETC.
28.	BETA-LACTAM ANTIBIOTICS (INCLUDING COMBINATION PRODUCTS)
29.	BISPHOSPHONATE (ALENDRONATE, CLODRONATE, IBANDRONIC ACID, PAMIDRONATE, RISEDRONATE, ZOLEDRONIC ACID)
30.	BLACK COHOSH (*CIMICIFUGA RACEMOSA*)
31.	BORTEZOMIB
32.	BOSWELLIA SPP.
33.	BROMHEXINE
34.	BROMPHENIRAMINE
35.	CAMPHOR
36.	CARBAMAZEPINE
37.	CARBIMAZOLE OR METHIMAZOLE (THIAMAZOLE)
38.	CARBOCISTEINE
39.	CEFTRIAXONE
40.	CETIRIZINE
41.	*CHELIDONIUM MAJUS*
42.	CHITOSAN
43.	CHLORHEXIDINE
44.	CHLORPHENIRAMINE
45.	CHORIONIC GONADOTROPHIN
46.	CLEMASTINE

47.	CLARITHROMYCIN
48.	CLINDAMYCIN
49.	CLOPIDOGREL
50.	CLOZAPINE
51.	COBICISTAT
52.	CODEINE
53.	COLCHICINE
54.	CORTICOSTEROID
55.	COX-2 INHIBITORS
56.	CYPROTERONE ACETATE
57.	CYPROTERONE ACETATE WITH ETHINYLESTRADIOL IN COMBINATION
58.	CYTOTOXIC AGENT
59.	DECITABINE
60.	DEXBROMPHENIRAMINE
61.	DEXTROMETHORPHAN
62.	DICLOFENAC SODIUM
63.	DICLOFENAC (SYSTEMIC FORMULATION)
64.	DICLOFENAC (ALL PRODUCTS EXCEPT PRODUCTS FOR CUTANEOUS USE)
65.	DICYCLOMINE
66.	DIPHENHYDRAMINE
67.	DIPHENOXYLATE
68.	DOMPERIDONE
69.	DOPAMINERGIC INGREDIENT
70.	DOXYCYCLINE
71.	EFAVIRENZ
72.	EPHEDRINE

73.	ERYTHROMYCIN
74.	ETHINYLESTRADIOL
75.	ETORICOXIB
76.	FAMOTIDINE
77.	FIBRATES
78.	FILGRASTIM
79.	FLUCLOXACILLIN
80.	FLUCONAZOLE
81.	FLUORIDE
82.	FLUOROQUINOLONE
83.	GABAPENTIN
84.	GADOBENIC ACID
85.	GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING
86.	GAMAT/ STICHOPUS spp.
87.	GENTAMICIN TOPICAL PREPARATIONS
88.	GINKGO BILOBA/ GINKGO EXTRACT
89.	GINSENG
90.	GLUCOSAMINE
91.	HIV PROTEASE INHIBITORS
92.	HYDROCHLOROTHIAZIDE
93.	HYDROQUINONE
94.	HYOSCINE
95.	IMMUNOSUPPRESANTS
96.	INSULIN (INCLUDING COMBINATION PRODUCTS)
97.	INGREDIENTS DERIVED FROM SEAFOOD
98.	INTERFERON ALPHA

99.	INTERFERON BETA
100.	IODINATED CONTRAST MEDIA
101.	ISONIAZID
102.	KAOLIN, PECTIN, KAOLIN-PECTIN
103.	KETOCONAZOLE
104.	KETOROLAC TROMETHAMOL (KETOROLAC TROMETHAMINE)
105.	LAMOTRIGINE
106.	LENOGRASTIM
107.	LEVETIRACETAM
108.	LEVONORGESTREL
109.	LINCOMYCIN
110.	LIQUID PARAFFIN
111.	LOPERAMIDE
112.	LOVASTATIN
113.	MEFLOQUINE
114.	MELALEUCA LEUCADENDRA
115.	MESALAZINE
116.	METFORMIN
117.	METHYL SALICYLATE
118.	METHYLCARBOCYSTEINE (MECYSTEINE)
119.	METHYLPHENIDATE HCL
120.	METOCLOPRAMIDE
121.	METRONIDAZOLE
122.	MICONAZOLE
123.	MIDAZOLAM
124.	MINOCYCLINE

125.	MINOXIDIL
126.	MIRTAZAPINE
127.	MOMORDICA CHARANTIA
128.	MONTELUKAST
129.	MYCOPHENOLATE (MYCOPHENOLATE MOFETIL AND MYCOPHENOLIC ACID)
130.	NEVIRAPINE
131.	NIFEDIPINE
132.	NITRATES
133.	NORADRENALINE
134.	NORFLOXACIN
135.	NORMAL GLOBULIN
136.	NOSCAPINE
137.	NONSTEROIDAL ANTI-INFLAMMATORY DRUG (NSAID)
138.	OLANZAPINE
139.	ONDANSETRON
140.	OPIOID
141.	OSELTAMIVIR
142.	PALIPERIDONE
143.	PARACETAMOL
144.	PARACETAMOL WITH CAFFEINE IN COMBINATION
145.	PARENTERAL NUTRITION CONTAINING AMINO ACIDS AND/OR LIPIDS (INDICATED FOR USE IN PEDIATRIC POPULATION AGED UNDER 2 YEARS)
146.	PEGFILGRASTIM
147.	*PELARGONIUM SIDOIDES*
148.	PEMETREXED
149.	PENICILLIN
150.	PHENIRAMINE

151.	PHENYLEPHRINE
152.	PIROXICAM
153.	PRAVASTATIN
154.	PREDNISONE AND PREDNISOLONE
155.	PROMETHAZINE HCL
156.	PROPAFENONE
157.	PROPOFOL
158.	PROPOLIS (ORAL)
159.	PROPOLIS (TOPICAL)
160.	PROPYLTHIOURACIL
161.	PSEUDOEPHEDRINE
162.	PROTON PUMP INHIBITORS (PPI)
163.	PSYCHOTROPIC PRODUCTS
164.	PSYLLIUM/ PLANTAGO (SEED/ HUSK)
165.	RED YEAST RICE (MONASCUS PURPUREUS)
166.	RETINOID (ORAL)
167.	RETINOIDS (ORAL) INDICATED FOR TREATMENT OF SKIN DISEASES
168.	RETINOIDS (TOPICAL)
169.	RISPERIDONE
170.	ROCURONIUM
171.	ROSIGLITAZONE
172.	ROSUVASTATIN
173.	ROXITHROMYCIN
174.	ROYAL JELLY
175.	SACCHAROMYCES BOULARDII
176.	SALBUTAMOL

177.	SALICYLIC ACID (NATURALLY OCCURING IN PLANTS E.G. WILLOW SALIX SPP)
178.	SEDATIVE – HYPNOTIC PRODUCTS
179.	SELENIUM SULPHIDE
180.	SENNA (CASSIA SPP.) – fruit/ pod/ semen and leaf and Rhubarb/ Radix et Rhizoma Rhei/ Rheum Palmatum/ Rheum Officinalis – root part
181.	SIMVASTATIN
182.	SODIUM GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS
183.	SODIUM METABISULPHITE (EXCIPIENT)
184.	SODIUM VALPROATE
185.	ST. JOHN'S WORT *(Hypericum perforatum)*
186.	STATINS
187.	STRONTIUM RANELATE
188.	SUCCINYLATED GELATIN (MODIFIED FLUID GELATIN)
189.	SULFASALAZINE
190.	SULPHONAMIDES/ TRIMETHOPRIM
191.	SYNTHETIC SALMON CALCITONIN
192.	TABEBUIA SPP. (PAU D'ARCO)
193.	TEMOZOLAMIDE
194.	TERBUTALINE
195.	TESTOSTERONE
196.	TETRACYCLINE SYRUP
197.	THIOMERSAL
198.	THROMBOLYTIC AGENTS
199.	TIAPROFENIC ACID
200.	TOPIRAMATE
201.	TRAMADOL

202.	TRIMETAZIDINE
203.	TRIPROLIDINE
204.	VARENICLINE
205.	VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) INHIBITORS
206.	VITAMIN K
207.	WARFARIN

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
1.	**5-ALPHA REDUCTASE INHIBITOR (5-ARI)** The following statement shall be included in the package inserts of products containing 5-ARI: **1.1 PRODUCT CONTAINING FINASTERIDE 5MG** **WARNINGS AND PRECAUTIONS** **Increased Risk of High-Grade Prostate Cancer** Men aged 55 and over with a normal digital rectal examination and PSA ≤3.0 ng/mL at baseline taking finasteride 5 mg/day in the 7-year Prostate Cancer Prevention Trial (PCPT) had an increased risk of Gleason score 8-10 prostate cancer (finasteride 1.8% vs placebo 1.1%). Similar results were observed in a 4-year placebo-controlled clinical trial with another 5-alpha reductase inhibitor (dutasteride, AVODART) (1% dutasteride vs 0.5% placebo). 5-alpha reductase inhibitors may increase the risk of development of high-grade prostate cancer. Whether the effect of 5-alpha reductase inhibitors to reduce prostate volume, or study-related factors, impacted the results of these studies has not been established. **Increased Risk of Breast Cancer** Breast cancer has been reported in men taking finasteride 5 mg during the post-marketing period. Physicians should instruct their patients to promptly report any changes in their breast tissue such as lumps, pain, gynaecomastia or nipple discharge. **ADVERSE EFFECTS/ UNDESIRABLE EFFECTS: POST MARKETING EXPERIENCE** Male breast cancer **1.2 PRODUCT CONTAINING FINASTERIDE 1MG** **WARNINGS AND PRECAUTIONS** **Increased Risk of High-Grade Prostate Cancer** Men aged 55 and over with a normal digital rectal examination and PSA ≤3.0 ng/mL at baseline taking finasteride 5 mg/day (5 times the dose of [Brand Name]) in the 7-year Prostate Cancer Prevention Trial (PCPT) had an increased risk of Gleason score 8-10 prostate cancer (finasteride 1.8% vs placebo 1.1%). Similar results were observed in a 4-year placebo-controlled clinical trial with another 5-alpha reductase inhibitor (dutasteride, AVODART) (1% dutasteride vs 0.5% placebo).

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	5-alpha reductase inhibitors may increase the risk of development of high-grade prostate cancer. Whether the effect of 5-alpha reductase inhibitors to reduce prostate volume, or study-related factors, impacted the results of these studies has not been established. **Increased Risk of Breast Cancer** Breast cancer has been reported in men taking finasteride 1 mg during the post-marketing period. Physicians should instruct their patients to promptly report any changes in their breast tissue such as lumps, pain, gynaecomastia or nipple discharge. **ADVERSE EFFECTS/ UNDESIRABLE EFFECTS: POST MARKETING EXPERIENCE** Male breast cancer **1.3 <u>PRODUCT CONTAINING DUTASTERIDE</u>** **WARNINGS AND PRECAUTIONS** **Increased Risk of High-Grade Prostate Cancer** In men aged 50 to 75 years with a prior negative biopsy for prostate cancer and a baseline PSA between 2.5 ng/mL and 10.0 ng/mL taking AVODART in the 4-year Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, there was an increased incidence of Gleason score 8-10 prostate cancer compared with men taking placebo (AVODART 1.0% versus placebo 0.5%). In a 7-year placebo-controlled clinical trial with another 5-alpha reductase inhibitor (finasteride 5 mg, PROSCAR), similar results for Gleason score 8-10 prostate cancer were observed (finasteride 1.8% versus placebo 1.1%). 5-alpha reductase inhibitors may increase the risk of development of high-grade prostate cancer. Whether the effect of 5-alpha reductase inhibitors to reduce prostate volume, or study-related factors, impacted the results of these studies has not been established. **References:** **Directive No. 9, 2011**. ***Bil. (19) dlm. BPFK/PPP/01/03 Jilid 1***. *Direktif Untuk Memuatkan Kenyataan Amaran Berkaitan Dengan Risiko High-Grade Prostate Cancer dalam Sisip Bungkusan Semua Produk 5-Alpha Reductase Inhibitor (5-ARI)* **Directive No. 3, 2012.** ***Bil. (64) dlm. BPFK/PPP/01/03 Jilid 1***. *Direktif Untuk Mengemaskini Sisip Bungkusan Produk Yang Mengandungi Finasteride Dengan Memuatkan Amaran Berkaitan dengan Risiko Kanser Payudara Di Kalangan Pesakit Lelaki*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
2.	**ABIRATERONE** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing Abiraterone; **Package Insert** **a) Warnings and Precautions** Hypoglycaemia Cases of hypoglycaemia have been reported when [product name] was administered to patients with pre-existing diabetes receiving pioglitazone or repaglinide; therefore, blood sugar should be measured frequently in patients with diabetes. **b) Interactions:** In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone was increased by 46% and the AUCs for M-III and M-IV, the active metabolites of pioglitazone, each decreased by 10% when pioglitazone was given together with a single dose of 1000mg abiraterone acetate. Patients should be monitored for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly. Examples of medicinal products metabolized by CYP2C8 include pioglitazone and repaglinide. **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [product name]:** Taking other medicines Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is important because [product name] may increase the effects of a number of medicines including some medicines for diabetes. Your doctor may want to change the dose of these medicines. **Reference: Directive No. 2, 2021.** ***NPRA.600-1/9/13 (12)*** *Direktif Untuk Semua Produk Yang Mengandungi Abiraterone: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Hypoglycaemia Akibat Interaksi Ubat*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
3.	**ACE INHIBITORS** The following statement shall be included in the package inserts of products containing ACE inhibitors: **WARNINGS AND PRECAUTIONS** • INCREASED RISK OF BIRTH DEFECTS, FOETAL AND NEONATAL MORBIDITY AND DEATH WHEN USED THROUGHOUT PREGNANCY **USE IN PREGNANCY** • INCREASED RISK OF BIRTH DEFECTS, FOETAL AND NEONATAL MORBIDITY AND DEATH WHEN USED THROUGHOUT PREGNANCY **Reference:** ***Circular Bil. (65) dlm. BPFK/02/5/1.3*** *Pernyataan Amaran Pada Sisip Bungkusan Bagi Semua Produk yang Mengandungi ACE Inhibitors Sebagai Bahan Tunggal Atau Kombinasi*
4.	**ACETAZOLAMIDE** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing Acetazolamide; **Package Insert** **a) Warnings and Precautions:** Adverse reactions common to all sulfonamide derivatives may occur such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), erythema multiforme (EM) and acute generalised exanthematous pustulosis (AGEP). If signs of serious reactions or hypersensitivity occur, discontinue use of this preparation. **b) Adverse Effects / Undesirable Effects:** Skin and Subcutaneous Tissue Disorders Frequency not known: Severe skin reactions [including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), erythema multiforme (EM) and acute generalised exanthematous pustulosis (AGEP)] **Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects:**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	[Product name] may cause severe allergy and serious skin reactions. Stop using [Product name] and seek medical assistance immediately if you experience any of the following symptoms: • severe skin reaction: skin reddening, blisters, rash, fever, sore throat or eye irritation **Reference: Directive No. 16, 2018.** ***BPFK/PPP/07/25 (16) Jld. 2*** *Direktif Untuk Semua Produk Yang Mengandungi Acetazolamide: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Severe Cutaneous Adverse Reactions (SCARs)*
5.	**ACETYLCYSTEINE** 5.1 The following warning shall be included in the package inserts of products containing Acetylcysteine : **CONTRAINDICATIONS** Contraindicated in children below two (2) years of age. **Reference: Directive No. 11, 2010.** ***Bil. (7) dlm. BPFK/PPP/01/03 Jilid 1*** *Kemaskini Kenyataan Amaran "Contraindicated In Children Under 2 Years Of Age" Yang Wajib Dimuatkan Pada Sisip Bungkusan Semua Produk Carbocysteine, Acetylcysteine Dan Methylcarbocysteine (Mecysteine)* 5.2 The following statements shall be included in the label, package insert and Consumer Medication Information Leaflet (RiMUP) for products containing acetylcysteine; **5.2.1 Injectable products with the indication as antidote for paracetamol overdose** **Package Insert** **a) Warnings and Precautions:** Hypersensitivity Reactions Serious acute hypersensitivity reactions during acetylcysteine administration including rash, hypotension, wheezing, and/or shortness of breath, have been observed in patients receiving intravenous acetylcysteine for paracetamol overdose and occurred soon after initiation of the infusion (see Adverse Effects/ Undesirable Effects). If a severe hypersensitivity reaction occurs, immediately stop the infusion of acetylcysteine and initiate appropriate treatment.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Acute flushing and erythema of the skin may occur in patients receiving acetylcysteine intravenously. These reactions usually occur 15 to 60 minutes after initiating the infusion and often resolve spontaneously despite continued infusion of acetylcysteine. If a reaction to acetylcysteine involves more than simply flushing and erythema of the skin, it should be treated as a hypersensitivity reaction. Management of less severe hypersensitivity reactions should be based upon the severity of the reaction and include temporary interruption of the infusion and/or administration of antihistaminic drugs. The acetylcysteine infusion may be carefully restarted after treatment of the hypersensitivity symptoms has been initiated; however, if the hypersensitivity reaction returns upon re-initiation of treatment or increases in severity, acetylcysteine should be discontinued and alternative patient management should be considered. **b) Adverse Effects / Undesirable Effects:** <u>Immune System Disorders:</u> Anaphylactic/ anaphylactoid reaction <u>Skin and Subcutaneous Tissue Disorders:</u> Severe cutaneous adverse reactions (SCAR) e.g. erythema multiforme, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). In most of these cases reported at least one other drug was administered at the same time, which may have possibly enhanced the described mucocutaneous effects. **5.2.2 All other products (not include Injectable products for treatment of paracetamol overdose)** **<u>Label</u>** [Product name] may cause severe allergy and serious skin reactions. Stop using [Product name] and seek medical assistance immediately if you experience any of the following symptoms: • Severe allergy: breathing difficulties, light headedness, skin swellings or rash. • Severe skin reaction: skin reddening, blisters, rash, fever, sore throat or eye irritation. **<u>Package Insert</u>** **Adverse Effects / Undesirable Effects:** <u>Immune System Disorders:</u> Anaphylactic / anaphylactoid reaction

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Skin and Subcutaneous Tissue Disorders: Severe cutaneous adverse reactions (SCAR) e.g. erythema multiforme, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). In most of these cases reported at least one other drug was administered at the same time, which may have possibly enhanced the described mucocutaneous effects. **Consumer Medication Information Leaflet (RiMUP)** **Side Effects:** [Product name] may cause severe allergy and serious skin reactions. Stop using [Product name] and seek medical assistance immediately if you experience any of the following symptoms: • Severe allergy: breathing difficulties, light headedness, skin swellings or rash. • Severe skin reaction: skin reddening, blisters, rash, fever, sore throat or eye irritation. **Reference: Directive No. 14, 2018.** ***BPFK/PPP/07/25 (14) Jld. 2*** *Direktif Untuk Semua Produk Yang Mengandungi Carbocisteine dan Acetylcysteine: Pengemaskinian Label, Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Anaphylactic/ Anaphylactoid Reaction dan Severe Cutaneous Adverse Reactions (SCARs)*
6.	**ACETYLSALICYLIC ACID (ASPIRIN)** For products containing Acetylsalicylic acid, the following warning shall be included on the labels in two languages (*Bahasa Malaysia* and English): ***AMARAN*** *TIDAK BOLEH DIBERI KEPADA KANAK-KANAK BERUMUR KURANG DARIPADA 16 TAHUN.* **WARNING** NOT TO BE GIVEN TO CHILDREN UNDER 16 YEARS OF AGE.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
7.	**ACTIVATED CHARCOAL/ ATTAPULGITE** 7.1 The following boxed warning shall be included on the labels of products containing Activated charcoal/ attapulgite: **NOT RECOMMENDED FOR TREATMENT OF DIARRHOEA IN CHILDREN UNDER 6 YEARS OF AGE** 7.2 The following statements shall be included in the package inserts of products containing Activated charcoal/ attapulgite: **Not recommended for treatment of diarhoea in children under 6 years of age** **WARNINGS AND PRECAUTIONS** Activated charcoal/ attapulgite may interfere with the absorption of other drugs, including antibiotics, when administered concurrently. Appropriate fluid and electrolyte therapy should be given to protect against dehydration. Oral rehydration therapy which is the use of appropriate fluids including oral rehydration salts remains the most effective treatment for dehydration due to diarrhoea. The intake of as much of these fluids as possible is therefore imperative.
8.	**ALBENDAZOLE & BENZIMIDAZOLE ANTIHELMINTICS** The following statement shall be included on the labels and in the package inserts of products containing Albendazole or Benzimidazole antihelmintics: **SHOULD NOT BE ADMINISTERED DURING CONFIRMED OR SUSPECTED PREGNANCY**
9.	**ALFALFA (*MEDICAGO SATIVA*)** The following boxed warning shall be included on the labels of products containing Alfalfa (*Medico sativa*): This product contains **Alfalfa** (*Medico sativa*). Individual with a predisposition to **systemic lupus erythematosus** should consult their physician before consuming this product.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
10.	**ALLOPURINOL** The following statement shall be included in the package inserts of products containing Allopurinol: **WARNINGS AND PRECAUTIONS** Allopurinol should be discontinued at the first appearance of skin rash or other signs which may indicate an allergic reaction. Hypersensitivity to allopurinol usually appears after some weeks of therapy, and more rarely immediately after beginning treatment. In some instances, a skin rash may be followed by more severe reactions such as exfoliative, urticarial and purpuric lesion as well as Stevens-Johnson syndrome, and/or generalized vasculitis, irreversible hepatotoxicity and even death.
11.	**AMBROXOL** The following warning shall be included in the package insert, label and Consumer Medication Information Leaflet (RiMUP) of products containing Ambroxol: **Package Insert** **a) Warnings and Precautions:** Very rare cases of chronically associated severe skin impairments such as Stevens Johnson Syndrome, Toxic Epidermal Necrolysis (TEN), Erythema Multiforme (EM) and Acute Generalized Exanthematous Pustulosis (AGEP) have been reported. In most cases, these could be explained by the severity of the underlying disease or concomitant administration of another drug. In the early stages of such severe skin reactions, initially only nonspecific flu-like symptoms appear, e.g. fever, arthralgia, runny nose, cough, and sore throat. If skin or mucous membrane damage occurs, seek medical advice immediately and discontinue treatment as a precaution. **b) Adverse Effects/Undesirable Effects:** Immune System Disorders Frequency not known: Anaphylactic reactions including anaphylactic shock. Skin and Subcutaneous Skin Disorders Frequency not known: Severe skin reactions (including Stevens Johnson syndrome, Toxic epidermal necrolysis (TEN), Erythema Multiforme (EM) and Acute Generalized Exanthematous Pustulosis (AGEP).

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Label and Consumer Medication Information Leaflet (RiMUP) **a) Side Effects** [Product name] may cause severe allergy and serious skin reactions. Stop using [Product name] and seek medical assistance immediately if you experience any of the following symptoms: 1) severe allergy: breathing difficulties, light headedness, skin swellings or rash 2) severe skin reaction: skin reddening, blisters, rash, fever, sore throat or eye irritation **Reference: Directive No. 1, 2018.** ***BPFK/PPP/07/25 (1) Jld. 2*** *Direktif Untuk Semua Produk Yang Mengandungi Ambroxol dan Bromhexine: Pengemaskinian Label, Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Amaran Kesan Advers Anafilaksis dan Severe Cutaneous Adverse Reactions (SCARs)*
12.	**AMIODARONE** The following boxed warning shall be included on the package inserts of products containing Amiodarone: This product is to be used only by a registered medical practitioner with experience in cardiology.
13.	**AMOXICILLIN** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing Amoxicillin (including combination products); **Package Insert** **a) Adverse Effects/ Undesirable Effects:** Skin and subcutaneous tissue disorders: Frequency 'very rare': Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Consumer Medication Information Leaflet (RiMUP) **a) Side Effects:** Stop taking [product name] and contact your doctor immediately if you experience any of the following: • Serious allergic reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). DRESS appears initially as flu-like symptoms with a rash on the face and then with an extended rash, high temperature and enlarged lymph nodes. **Reference: Directive No. 8, 2018.** ***BPFK/PPP/07/25 (8) Jld. 2*** *Direktif Untuk Semua Produk Yang Mengandungi Amoxicillin Termasuk Kombinasi: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Memperkukuhkan Maklumat Berkaitan Severe Cutaneous Adverse Reactions (SCARs) Pada Bahagian Warnings & Precautions dan Amaran Berkaitan Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS) Pada Bahagian Side Effects*
14.	**ANASTROZOLE** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing anastrozole: **Package Insert** **a) Adverse Effects/ Undesirable Effects:** Psychiatric disorders Frequency 'very common': Depression **Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects:** Frequency 'very common': Depression **Reference: Directive No. 21, 2021**. ***NPRA.600-1/9/13(31)*** *Direktif Untuk Semua Produk Yang Mengandungi Anastrozole: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Depression*
15.	**ANTIDEPRESSANTS** The following statement shall be included in the package inserts of products used as antidepressants: **WARNINGS AND PRECAUTIONS**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Suicidality in Children and Adolescents • Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. • Anyone considering the use of an antidepressant in a child or adolescent for any clinical use must balance the risk of increased suicidality with the clinical need. • Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. • Families and caregivers should be advised to closely observe the patient and to communicate with the prescriber. • The indication(s) approved in paediatric for the particular drug should be clearly stated / included. **Reference:** ***Bil.(41)dlm. BPFK/02/5/1.3*** *Keputusan Pihak Berkuasa Kawalan Dadah (PBKD) Berhubung Tambahan Amaran Berkaitan Dengan "Suicidality In Children and Adolescents Treated With Antidepressants"* **CITALOPRAM, DESVENLAFAXINE, DULOXETINE, ESCITALOPRAM, FLUOXETINE, FLUVOXAMINE, PAROXETINE, SERTRALINE, VENLAFAXINE AND VORTIOXETINE** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine and vortioxetine; **Package Insert** **a) Pregnancy and lactation:** Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth. *An additional statement should also be included in the package insert of vortioxetine: Although no studies have investigated an association between vortioxetine treatment and postpartum haemorrhage, there is a potential risk, taking into account the related mechanism of action. **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use <product name>:** Before you start to use it: If you take <product name> near the end of your

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	pregnancy there may be an increased risk of heavy vaginal bleeding shortly after birth, especially if you have a history of bleeding disorders. Your doctor should be aware that you are taking <product name> so they can advise you. **Reference: Directive No. 23, 2021.** ***NPRA.600-1/9/13 (33)*** *Direktif Untuk Semua Produk Yang Mengandungi Citalopram, Desvenlafaxine, Duloxetine, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, Venlafaxine dan Vortioxetine: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Postpartum Haemorrhage (PPH)*
16.	**ANTIEPILEPTICS** The following statement shall be included in the package inserts of products used as antiepileptics: **WARNINGS AND PRECAUTIONS** Potential for an increase in risk of suicidal thoughts or behaviors. **Reference:** ***Bil. (43) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Berkaitan Dengan "Potential for an Increase in Risk of Suicidal Thoughts or Behaviours" yang Perlu Dimuatkan Pada Sisip Bungkusan Produk Antiepileptik*
17.	**ANTIPSYCHOTIC AGENTS** **17.1 ALL ANTIPSYCHOTIC AGENTS** The following statement shall be included in the package inserts of products containing antipsychotic: **PREGNANCY AND LACTATION** Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalisation. [BRAND NAME] should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. **Reference:** ***Bil. (16) dlm. BPFK/PPP/01/03 Jilid 1*** *Directif Kenyataan Amaran Berkaitan Dengan Risiko Extrapyrimidal and/or Withdrawal Symptoms Bagi Neonat Yang Terdedah Kepada Produk Antipsikotik Semasa Trimester Ketiga Kehamilan Pada Sisip Bungkusan Semua Produk Antipsikotik* **17.2 ATYPICAL ANTIPSYCHOTIC AGENTS** The following statements shall be included in the package insert and Consumer

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Medication Information Leaflet (RiMUP) for products containing Atypical Antipsychotic Agent; **Package Insert** **a) Warnings and Precautions:** **[replace *Direktif Bil. (31) dlm BPFK/02/5/1.3: Tambahan amaran berkaitan dengan hyperglycemia bagi keluaran 'atypical antipsychotic agents' bertarikh 20 Julai 2004*]** Hyperglycaemia and Diabetes Mellitus: Hyperglycaemia in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotics use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given this confounders, the relationship between atypical antipsychotic use and hyperglycaemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycaemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycaemia-related adverse events in patients treated with atypical antipsychotics are not available. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug. **b) Adverse Effects/Undesirable Effects:** Nervous System Disorders: Restless legs syndrome

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Respiratory, Thoracic and Mediastinal Disorders: Sleep apnoea* *Atypical antipsychotic drugs, such as <active ingredient>, have been associated with cases of sleep apnoea, with or without concomitant weight gain. In patients who have a history of or are at risk for sleep apnoea, [product name] should be prescribed with caution. Renal and Urinary Disorders: Urinary retention **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [product name]:** Before you start to use it Talk to your doctor or pharmacist if you: • have or are at a risk of having diabetes (e.g. being overweight or a family history of diabetes). Your doctor should check your blood sugar before you start taking [product name] and regularly during treatment. **b) Side Effects:** Talk to your doctor or pharmacist if you experience: • Increases in blood sugar level and/or symptoms of high blood sugar (e.g. increased thirst, increased hunger, and frequent urination) • Unpleasant leg sensations and an intense urge to move the legs (restless legs syndrome) • Trouble breathing during sleep (sleep apnoea) • Difficulty or inability to pass urine (urinary retention) **Reference: Directive No. 26, 2018.** *BPFK/PPP/07/25 (26) Jld. 2 Direktif Untuk Semua Produk Yang Mengandungi Atypical Antipsychotic Agent: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RIMUP) Dengan Maklumat Berkaitan Risiko Restless Legs Syndrome, Sleep Apnoea, Urinary Retention, Hyperglycaemia dan Diabetes Mellitus*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
18.	**ARGININE** The following statement shall be included on the labels and in the package inserts of oral preparations containing Arginine for **health supplement products**: **WARNINGS AND PRECAUTIONS** Arginine is not recommended for patients following a heart attack. **Reference:** ***Bil. (64) dlm. BPFK/02/5/1.3*** *Pernyataan Amaran Pada Lebal dan Sisip Bungkusan Produk Suplemen Kesihatan Oral Yang Mengandungi Arginine Berkaitan Dengan "Arginine is not recommended for patients following a heart attack"*
19.	**ARIPIPRAZOLE** The following statements shall be included in the package insert and RiMUP of products containing Aripiprazole: **Package Insert** **a) Warnings and Precautions:** Pathological gambling and impulse-control problems Patients can experience increased urges, particularly for gambling, and the inability to control these urges while taking aripiprazole. Other urges, reported include: increased sexual urges, compulsive shopping, binge or compulsive eating, and other impulsive and compulsive behaviours. It is important for prescribers to ask patients or their caregivers specifically about the development of new or increased gambling urges, or other urges, while being treated with aripiprazole. It should be noted that impulse-control symptoms can be associated with the underlying disorder; however, in some cases urges were reported to have stopped when the dose was reduced or the medication was discontinued. Patients who are at higher risk for impulse-control problems (e.g. personal or family history of obsessive-compulsive disorder, impulse-control disorder, bipolar disorder, impulsive personality, alcoholism, drug abuse or other addictive behaviours) would require closer monitoring for new or worsening of uncontrollable urges. Impulse-control problems may result in harm to the patient and others if not recognised. Consider dose reduction or stopping the medication if a patient develops such urges while taking aripiprazole. **b) Adverse Effects/Undesirable Effects:** Psychiatric disorders Pathological gambling, hypersexuality, impulse-control problems (See Section Warnings and Precautions).

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Consumer Medication Information Leaflet (RiMUP) **a) Before you use [product name]** Before you start to use it Talk to your doctor or pharmacist if you have: • a history of excessive gambling or other unusual urges (e.g. increased sexual urges, binge or compulsive eating, and compulsive shopping). **b) Side effects:** Side effects may include: • Excessive gambling or other unusual urges, such as increased sexual urges, binge or compulsive eating, and compulsive shopping. If you or your family members notice that you are having unusual urges or behaviours, talk to your doctor or pharmacist. **Reference: Directive No. 22, 2017.** ***BPFK/PPP/07/25 (27) Jld. 1*** *Direktif Untuk Semua Produk Yang Mengandungi Aripripazole: Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Kesan Advers Pathological Gambling dan Impulse-Control Problems*
20.	**ASPARTAME** The following statement shall be included on the labels and in the package inserts of products containing Aspartame: **WARNING** Unsuitable for phenylketonurics.
21.	**ATORVASTATIN** The following statement shall be included in the package inserts of products containing Atorvastatin: **DOSAGE AND ADMINISTRATION** Dosage in Patients Taking Cyclosporine, Clarithromycin, Itraconazole, or Certain Protease Inhibitors In patients taking cyclosporine or the HIV protease inhibitors (tipranavir plus ritonavir) or the hepatitis C protease inhibitor (telaprevir), therapy with [Product Name] should be avoided.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	In patients with HIV taking lopinavir plus ritonavir, caution should be used when prescribing [Product Name] and the lowest dose necessary employed. In patients taking clarithromycin, itraconazole, or in patients with HIV taking a combination of saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, therapy with [Product Name] should be limited to 20 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed. In patients taking the HIV protease inhibitor nelfinavir or the hepatitis C protease inhibitor boceprevir, therapy with [Product Name] should be limited to 40 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed. **WARNINGS AND PRECAUTIONS** Skeletal Muscle Effects Physicians considering combined therapy with atorvastatin and fibrates, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-modifying doses of niacin (≥1g/day) should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Therefore, lower starting and maintenance doses of atorvastatin should also be considered when taken concomitantly with the aforementioned drugs. Temporary suspension of atorvastatin may be appropriate during fusidic acid therapy. All generic products containing Atorvastatin should update their package inserts respectively according to the innovator's information such as parts for Interactions, Pharmacokinetics and other parts deemed relevant. **Reference: Directive No. 10, 2014.** ***Bil. (17) dlm. BPFK/PPP/07/25*** *Direktif Untuk Semua Produk Atorvastatin: Mengehadkan Dos Penggunaan Atorvastatin Untuk Mengurangkan Risiko Kecederaan Otot*
22.	**AZITHROMYCIN** **22.1** The following statement shall be included in the package insert and RIMUP of **all products containing Azithromycin**: **Package Insert** **a) Warnings and Precautions** In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCARs) [e.g. Stevens-Johnson Syndrome (SJS), toxic

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP)], [product name] should be discontinued immediately and appropriate treatment should be urgently initiated. **b) Adverse Effects/ Undesirable Effects** Skin and Subcutaneous Tissue Disorders: Frequency not known: severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP). **Consumer Medication Information Leaflet (RiMUP)** **Side Effects** [Product name] may cause severe allergy and serious skin reactions. Stop using [Product name] and seek medical assistance immediately if you experience any of the following symptoms: • skin reddening, blisters, rash, fever, sore throat or eye irritation **22.2** The following statement shall be included in the package insert and RiMUP of **products containing azithromycin (except topical/ external and ophthalmic preparations);** **Package Insert** **a) Warnings and Precautions:** **Prolongation of the QT interval** Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with macrolides, including azithromycin (see section 4.8). Prescribers should consider the risk of QT prolongation, which can be fatal, when weighing the risks and benefits of azithromycin for at-risk groups including: • Patients with congenital or documented QT prolongation • Patients currently receiving treatment with other active substances known to prolong QT interval, such as antiarrhythmics of Classes IA and III, antipsychotic agents, antidepressants, and fluoroquinolones • Patients with electrolyte disturbance, particularly in cases of hypokalemia and hypomagnesemia • Patients with clinically relevant bradycardia, cardiac arrhythmia or cardiac insufficiency

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	• Elderly patients: elderly patients may be more susceptible to drug-associated effects on the QT interval Infantile hypertrophic pyloric stenosis (IHPS) has been reported following the use of azithromycin in infants (treatment up to 42 days of life). Parents and caregivers should be informed to contact their physician if vomiting and/ or irritability with feeding occurs. **b) Adverse Effects/Undesirable Effects:** Postmarketing Experience: Cardiac Disorders: Palpitations and arrhythmias including ventricular tachycardia have been reported. There have been rare reports of QT prolongation and torsades de pointes (see **Warnings and Precautions**). Gastrointestinal Disorders: infantile hypertrophic pyloric stenosis. **Consumer Medication Information Leaflet (RiMUP)** **Side Effects** If you notice that the child vomits and/or irritability with feeding occurs, contact doctor immediately as it may be due to the Infantile Hypertrophic Pyloric Stenosis (IHPS). **References:** **Directive No. 3, 2016**. ***Bil. (34) dlm. BPFK/PPP/07/25*** *Direktif Untuk Semua Produk Yang Mengandungi Azithromycin (Formulasi Sistemik): Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Kesan Advers QT Prolongation Dan Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS)* **Directive No. 28, 2017.** ***BPFK/PPP/07/25 (33) Jld.1*** *Direktif Untuk Semua Produk Yang Mengandungi Bahan Aktif Azithromycin Dan Erythromycin Kecuali Persediaan Topikal/ Eksternal Dan Ubat Untuk Kegunaan Mata: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Amaran Berkaitan Risiko Infantile Hypertrophic Pyloric Stenosis (IHPS)* **Directive No. 22, 2018.** ***Bil. (22) dlm. BPFK/PPP/07/25 Jld.2*** *Direktif Untuk Semua Produk Yang Mengandungi Azithromycin, Clarithromycin, Erythromycin dan Roxithromycin: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Severe Cutaneous Adverse Reactions (SCARs)*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
23.	**BEE POLLEN** The following statement shall be included on the labels and in the package inserts of products containing bee pollen: This product contains Bee Pollen and may cause severe allergic reactions, including fatal anaphylactic reactions in susceptible individuals. Asthma and allergy sufferers may be at greater risks.
24.	**BENZODIAZEPINE** The following statements shall be included in the package insert and RiMUP of pharmaceutical products containing benzodiazepine: **Package Insert** **a) Warnings and Precautions:** Risks from Concomitant Use with Opioids Profound sedation, respiratory depression, coma, and death may result from the concomitant use of [product name] with opioids. Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. If the decision is made to newly prescribe a benzodiazepine and an opioid together, prescribe the lowest effective dosages and minimum durations of concomitant use. If the decision is made to prescribe a benzodiazepine in a patient already receiving an opioid, prescribe a lower initial dose of the benzodiazepine than indicated in the absence of an opioid, and titrate based on clinical response. If the decision is made to prescribe an opioid in a patient already taking a benzodiazepine, prescribe a lower initial dose of the opioid, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when [product name] is used with opioids. Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the opioid have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	of the risk for overdose and death associated with the use of opioids (See Drug Interactions). **b) Interactions:** Opioids Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death. The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at μ-receptors, and benzodiazepines interact at $GABA_A$ sites. When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see Warnings and Precautions). Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation. **Consumer Medication Information Leaflet (RiMUP)** **a) Taking other medicines:** Taking [product name] with an opioid medicine (medicine to relieve pain) can depress your central nervous system. Inform your doctor if you are currently taking any opioid medicine. Seek medical attention immediately if you or the person taking this medication experience(s) symptoms of unusual dizziness or lightheadedness, extreme sleepiness, slowed or difficult breathing, or unresponsiveness. **Reference: Directive No. 23, 2017.** ***BPFK/PPP/07/25 (28) Jld. 1*** *Direktif Untuk Semua Produk Yang Mengandungi Opioid dan Benzodiazepin : Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Interaksi Ubat*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
25.	**BENZOYL PEROXIDE** The following statement shall be included on the labels and in the package inserts of products containing Benzoyl peroxide: **WARNING** Do not use this medication if you have sensitive skin or if you are sensitive to benzoyl peroxide. This product may cause irritation, characterized by redness, burning, itching, peeling, or possible swelling.
26.	**BENZYL ALCOHOL** The following statement shall be included on label and in package insert of parenteral products containing Benzyl alcohol: **As this preparation contains benzyl alcohol, its use should be avoided in children under two years of age.** **Not to be used in neonates.**
27.	**BERBERINE ALKALOIDS – NATURALLY OCCURING BERBERINE e.g. HYDRASTIS CANADENSIS (GOLDENSEAL), COPTIS CHINENSIS (COPTIS OR GOLDENTHREAD), FIBRAUREA CHLOROLEUCA etc.** The following statement shall be included on the label and in the package insert of products containing berberine alkaloid: **WARNING** Not to be taken by babies, children under 12 years of age, pregnant women or lactating mothers. Consult your practitioner if you have conditions such as: -Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency -Haemolytic anemia -Glaucoma -Diabetes -High Blood Pressure -History of cardiovascular disease -If you are using Paclitaxel, Cyclosporin, or other chemotherapeutic agents. **Reference:** ***Bil.(22)dlm.BPFK/PPP/06/12 Jld.26*** *Kawalan Produk Mengandungi Bahan Aktif Yang Mempunyai Berberine Secara Semulajadi*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
28.	**BETA-LACTAM ANTIBIOTICS (INCLUDING COMBINATION PRODUCTS)** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing beta-lactam antibiotics (including combination products); **Package Insert** **a) Warnings and Precautions:** Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients receiving therapy with beta-lactams. Before initiating therapy with [product name], careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, carbapenems or other beta-lactam agents. If an allergic reaction occurs, [product name] must be discontinued immediately and appropriate alternative therapy instituted. **Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects:** [Product name] may cause severe allergy and serious skin reactions. Stop using [product name] and seek medical assistance immediately if you experience any of the following symptoms: • skin reddening, blisters, rash, fever, sore throat or eye irritation **Reference: Directive No. 2, 2019.** ***BPFK/PPP/07/25 (2) Jld.3*** *Direktif Untuk Semua Produk Antibiotik Kumpulan Beta-Lactam Termasuk Kombinasi: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Severe Cutaneous Adverse Reactions (SCARs)*
29.	**BISPHOSPHONATE (ALENDRONATE, CLODRONATE, IBANDRONIC ACID, PAMIDRONATE, RISEDRONATE, ZOLEDRONIC ACID)** The following statement shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing Bisphosphonate (Alendronate, Clodronate, Ibandronic acid, Pamidronate, Risedronate, Zoledronic acid): **Package Insert** **WARNINGS AND PRECAUTIONS:** Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms including chronic ear infections. **ADVERSE EFFECTS / UNDESIRABLE EFFECTS:** Very rare: Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction). **Consumer Medication Information Leaflet (RiMUP)** **SIDE EFFECTS:** Very rare • Talk to your doctor if you have ear pain, discharge from the ear, and/or an ear infection. These could be signs of bone damage in the ear. **Reference: Directive No. 7, 2016.** ***BPFK/PPP/07/25(38)*** *Direktif Bagi Semua Produk Yang Mengandungi Bisphosphonate (Alendronate, Clodronate, Ibandronic Acid, Pamidronate, Risedronate, Zoledronic Acid) Dengan Risiko Kesan Advers Berkaitan Osteonecrosis of the External Auditory Canal*
30.	**BLACK COHOSH (*CIMICIFUGA RACEMOSA*)** The following statement shall be included on the labels and in the package inserts of products containing Black Cohosh (*Cimicifuga Racemosa*): **WARNING** Stop taking this product if signs and symptoms suggestive of liver injury develop such as tiredness, loss of appetite, yellowing of the skin and eyes or severe upper stomach pain with nausea and vomiting or dark urine and consult your doctor immediately. Patients using herbal medicinal products should tell their doctor about it. **Reference:** ***Bil. (61) dlm. BPFK/02/5/1.3*** *Pernyataan Amaran Pada Label dan Sisip Bungkusan Produk Tradisional/Semulajadi Yang Mengandungi Black Cohosh (Cimicifugae Racemosae) Berkaitan Dengan "Serious Hepatic Reactions"*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
31.	**BORTEZOMIB** The following statements shall be included in the package insert for products containing bortezomib: **Package Insert** **a) Adverse Effects/ Undesirable Effects:** Nervous system disorders Frequency 'rare': Guillain-Barré syndrome, Demyelinating polyneuropathy **Reference: Directive No. 20, 2021.** ***NPRA.600-1/9/13(30)*** *Direktif Untuk Semua Produk Yang Mengandungi Bortezomib: Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Risiko Guillain-Barré Syndrome dan Demyelinating Polyneuropathy*
32.	**BOSWELLIA SPP.** The following statement shall be included on label and package inserts of oral products containing *Boswellia spp:* **WARNING:** Please consult your doctor/pharmacist before using this product if you are on other medicines. **Reference: Directive No. 10, 2018.** ***BPFK/PPP/07/25(10)Jld.2*** *Direktif Penambahan Kenyataan Amaran Bagi Semua Produk Yang Mengandungi Boswellia Spp.*
33.	**BROMHEXINE** The following warning shall be included in the package insert, label and Consumer Medication Information Leaflet (RiMUP) of products containing Bromhexine : **Package Insert** **a) Warnings and Precautions:** Very rare cases of chronically associated severe skin impairments such as Stevens Johnson Syndrome, Toxic Epidermal Necrolysis (TEN), Erythema Multiforme (EM) and Acute Generalized Exanthematous Pustulosis (AGEP) have been reported. In most cases, these could be explained by the severity of the underlying disease or concomitant administration of another drug. In the

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	early stages of such severe skin reactions, initially only nonspecific flu-like symptoms appear, e.g. fever, arthralgia, runny nose, cough, and sore throat. If skin or mucous membrane damage occurs, seek medical advice immediately and discontinue treatment as a precaution. **b) Adverse Effects/Undesirable Effects:** Immune System Disorders Frequency not known: Anaphylactic reactions including anaphylactic shock. Skin and Subcutaneous Skin Disorders Frequency not known: Severe skin reactions (including Stevens Johnson syndrome, Toxic epidermal necrolysis (TEN), Erythema Multiforme (EM) and Acute Generalized Exanthematous Pustulosis (AGEP). **Label and Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects** [Product name] may cause severe allergy and serious skin reactions. Stop using [Product name] and seek medical assistance immediately if you experience any of the following symptoms: 1) severe allergy: breathing difficulties, light headedness, skin swellings or rash 2) severe skin reaction: skin reddening, blisters, rash, fever, sore throat or eye irritation **Reference: Directive No. 1, 2018.** ***BPFK/PPP/07/25 (1) Jld. 2*** *Direktif Untuk Semua Produk Yang Mengandungi Ambroxol dan Bromhexine : Pengemaskinian Label, Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Amaran Kesan Advers Anafilaksis dan Severe Cutaneous Adverse Reactions (SCARs)*
34.	**BROMPHENIRAMINE** The following statement shall be included on the labels and in the package inserts of liquid oral products containing Brompheniramine: **WARNING** When used for treatment of cough and cold: (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. **Reference:** ***Bil. (34) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
35.	**CAMPHOR** 1. The following boxed warning shall be included on the labels of products containing Camphor: CAN CAUSE CONVULSION **CONTRAINDICATED** IN CHILDREN BELOW 2 YEARS OF AGE. CAUTION MUST BE EXERCISED WHEN OLDER CHILDREN ARE TREATED **AVOID DIRECT** APPLICATION INTO THE NOSTRILS 2. The following warnings and precautions shall be included in the package insert of products containing Camphor: **WARNINGS AND PRECAUTIONS** This product is contraindicated in **children** below 2 years of age. Caution must be exercised when older children are treated. It is dangerous to place any camphor containing product into the nostril of children. A small amount applied this way may cause immediate collapse.
36.	**CARBAMAZEPINE** The following statement shall be included in the package insert of products containing Carbamazepine: Severe dermatologic reactions including Stevens - Johnson syndrome and toxic epidermal necrolysis (Lyell's Syndrome) have been reported with carbamazepine. Patients treated with carbamazepine should closely be monitored for signs of hypersensitivity reactions, particularly during the first month of therapy. Immediate discontinuation of therapy should be made when cutaneous reactions occur.
37.	**CARBIMAZOLE OR METHIMAZOLE (THIAMAZOLE)** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing carbimazole or methimazole (thiamazole): **Package Insert** **a) Contraindications:** Patients with a history of acute pancreatitis after administration of carbimazole or active metabolite, methimazole (thiamazole).

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	b) Warnings and Precautions: Carbimazole may cause white cell disorders such as neutropenia and agranulocytosis, which may be fatal if treatment with carbimazole is not stopped promptly. These reactions usually occur during the first 3 months of therapy, and in most cases, are reversible on stopping treatment. Since agranulocytosis can develop very rapidly, periodic leucocyte counts alone may not be effective in the early detection of these reactions. There have been post-marketing reports of acute pancreatitis in patients receiving carbimazole or its active metabolite, methimazole (thiamazole). In case of acute pancreatitis, carbimazole or methimazole (thiamazole) should be discontinued immediately. Carbimazole or methimazole (thiamazole) must not be given to patients with a history of acute pancreatitis after administration of carbimazole or its active metabolite methimazole (thiamazole). Re-exposure may result in recurrence of acute pancreatitis, with decreased time to onset. <u>Women of childbearing potential and pregnancy</u> Women of childbearing potential have to use effective contraceptive measures during treatment. The use of carbimazole or methimazole (thiamazole) in pregnant women must be based on the individual benefit/risk assessment. If carbimazole or methimazole (thiamazole) is used during pregnancy, the lowest effective dose without additional administration of thyroid hormones should be administered. Close maternal, foetal and neonatal monitoring is warranted. **c) Fertility, Pregnancy and Lactation:** <u>Women of childbearing potential and pregnancy</u> Women of childbearing potential have to use effective contraceptive measures during treatment (see Section Warnings and Precautions). <u>Pregnancy</u> Carbimazole or methimazole (thiamazole) crosses the placenta but, provided the mother's dose is within the standard range and her thyroid status is monitored; there is no evidence of neonatal thyroid abnormalities. Studies have shown that the incidence of congenital malformations is greater in the children of mothers whose hyperthyroidism has remained untreated than in those who have been treated with carbimazole or methimazole (thiamazole). However, cases of congenital malformations have been observed following the use of carbimazole or its active metabolite, methimazole (thiamazole) during pregnancy. A causal relationship of these malformations, especially choanal atresia and aplasia cutis congenita (congenital scalp defects), to transplacental exposure to carbimazole

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	and methimazole (thiamazole) cannot be excluded. Therefore, the use of carbimazole or methimazole (thiamazole) in non-pregnant women of childbearing potential should be based on individual risk/benefit assessment (see section Warnings and Precautions). Cases of renal, skull, cardiovascular congenital defects, exomphalos, gastrointestinal malformation, umbilical malformation and duodenal atresia have also been reported. Therefore, carbimazole or methimazole (thiamazole) should be used in pregnancy only when propylthiouracil is not suitable. If carbimazole or methimazole (thiamazole) is used in pregnancy, the dose must be regulated by the patient's clinical condition. The lowest dose possible should be used, and this can often be discontinued three or four weeks before term, in order to reduce the risk of neonatal complications. The blocking-replacement regimen should not be used during pregnancy since very little thyroxine crosses the placenta in the last trimester. Hyperthyroidism in pregnant women should be adequately treated to prevent serious maternal and foetal complications. Carbimazole or methimazole (thiamazole) is able to cross the human placenta. Based on human experience from epidemiological studies and spontaneous reporting, carbimazole or methimazole (thiamazole) is suspected to cause congenital malformations when administered during pregnancy, particularly in the first trimester of pregnancy and at high doses. Reported malformations include aplasia cutis congenita, craniofacial malformations (choanal atresia; facial dysmorphism), exomphalos, oesophageal atresia, omphalo-mesenteric duct anomaly, and ventricular septal defect. Carbimazole or methimazole (thiamazole) must only be administered during pregnancy after a strict individual benefit/risk assessment and only at the lowest effective dose without additional administration of thyroid hormones. If carbimazole or methimazole (thiamazole) is used during pregnancy, close maternal, foetal and neonatal monitoring is recommended (see section Warnings and Precautions). **d) Adverse Effects / Undesirable Effects:** SOC Gastrointestinal disorders Frequency “Not Known”: Acute pancreatitis

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Consumer Medication Information Leaflet (RiMUP) **a) Before you use [Product Name]:** When you must not use it: - Do not use [Product name] if you had inflammation of the pancreas (acute pancreatitis) after administration of carbimazole or thiamazole in the past. Before you start to use it: - [Product name] can cause harm to an unborn baby. If you can get pregnant, use reliable contraception from the time you start treatment and during treatment. - If you are pregnant, think you may be pregnant or are planning to have a baby, tell your doctor straight away. Your treatment with [product name] may need to be continued during pregnancy if the potential benefit outweighs the potential risk to you and your unborn baby. **b) While you are using it:** Things to be careful of: - Tell your doctor straight away if you develop fever or abdominal pain, which may be signs of inflammation of the pancreas (acute pancreatitis). [Product name] may need to be discontinued. **c) Side Effects:** - Inflammation of the pancreas (acute pancreatitis) **Reference: Directive No. 19, 2019.** ***BPFK/PPP/07/25 (19) Jld. 3*** *Direktif Untuk Semua Produk Yang Mengandungi Carbimazole atau Methimazole (Thiamazole): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RIMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Pankreatitis Akut (Acute Pancreatitis) dan Pengukuhan Maklumat Keselamatan Berkaitan Risiko Kecacatan Kongenital (Congenital Malformation)*
38.	**CARBOCISTEINE** The following statements shall be included in the label, package insert and Consumer Medication Information Leaflet (RiMUP) of products containing carbocisteine: **Label** [Product name] may cause severe allergy and serious skin reactions. Stop using [Product name] and seek medical assistance immediately if you experience any of the following symptoms: • Severe allergy: breathing difficulties, light headedness, skin swellings or rash. • Severe skin reaction: skin reddening, blisters, rash, fever, sore throat or eye irritation.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Package Insert **a) Adverse Effects/ Undesirable Effects:** Immune System Disorders: Anaphylactic / anaphylactoid reaction Skin and Subcutaneous Tissue Disorders: Severe cutaneous adverse reactions (SCAR) e.g. erythema multiforme, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). In most of these cases reported at least one other drug was administered at the same time, which may have possibly enhanced the described mucocutaneous effects. **b) Contraindications** Contraindicated in children below two (2) years of age. **Reference: Directive No. 11, 2010.** ***Bil. (7) dlm. BPFK/PPP/01/03 Jilid 1*** *Kemaskini Kenyataan Amaran "Contraindicated In Children Under 2 Years Of Age" Yang Wajib Dimuatkan Pada Sisip Bungkusan Semua Produk Carbocysteine, Acetylcysteine dan Methylcarbocysteine (Mecysteine)* **Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects:**]Product name] may cause severe allergy and serious skin reactions. Stop using [Product name] and seek medical assistance immediately if you experience any of the following symptoms: • Severe allergy: breathing difficulties, light headedness, skin swellings or rash. • Severe skin reaction: skin reddening, blisters, rash, fever, sore throat or eye irritation. **Reference: Directive No. 14, 2018.** ***BPFK/PPP/07/25 (14) Jld. 2*** *Direktif Untuk Semua Produk Yang Mengandungi Carbocisteine dan Acetylcysteine: Pengemaskinian Label, Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Anaphylactic/ Anaphylactoid Reaction dan Severe Cutaneous Adverse Reactions (SCARs)*
39.	**CEFTRIAXONE** The following statements shall be included in the package insert for products containing Ceftriaxone: **Package Insert** **CONTRAINDICATION**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Ceftriaxone is contraindicated in neonates (≤28 days of age) if they require (or are expected to require) treatment with calcium-containing intravenous solutions, including calcium-containing infusions such as parenteral nutrition, because of the risk of precipitation of ceftriaxone-calcium. **WARNINGS AND PRECAUTIONS** • In patients other than neonates, Ceftriaxone and calcium-containing solutions may be administered sequentially to one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid. • Diluents containing calcium, such as Ringer's solution or Hartmann's solution, are not to be used to reconstitute Ceftriaxone vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Ceftriaxone must not be administered simultaneously with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site, because precipitation of ceftriaxone-calcium can occur. **Reference:** ***Bil. (48) dlm. BPFK/PPP/01/03*** *Pindaan Pada Kenyataan Amaran Berkaitan Dengan "Potential Risk Associated with Concomitant Use Of Ceftriaxone With Calcium - Containing Intravenous Solutions" Yang Perlu Dimuatkan Pada Sisip Bungkusan Produk Ceftriaxone* **ADVERSE EFFECTS/ UNDESIRABLE EFFECTS** *Nervous system disorders* *Frequency 'not known': Encephalopathy** **Reversible encephalopathy has been reported with the use of ceftriaxone, particularly when high doses are administered in patients with renal impairment and additional predisposing factors such as older age, pre-existing central nervous system disorders.* **Reference: Directive No. 14, 2021**. ***NPRA.600-1/9/13(24)*** *Direktif Untuk Semua Produk Yang Mengandungi Ceftriaxone: Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Risiko Encephalopathy*
40.	**CETIRIZINE** The following statement shall be included in the package insert of products containing Cetirizine: **WARNINGS AND PRECAUTIONS** Activities Requiring Mental Alertness: In clinical trials the occurrence of somnolence has been reported in some patients taking Cetirizine: due caution should therefore be exercised when driving a car or operating potentially dangerous machinery.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
41.	***CHELIDONIUM MAJUS*** The following statement shall be included on the label of products containing *Chelidonium majus* in 2 languages (*Bahasa Melayu* and English) in bold font: **WARNING** This product may cause adverse reaction to the liver. ***AMARAN*** *Produk ini mungkin boleh menyebabkan kesan sampingan pada hepar (hati).* **Reference:** ***Bil. 17 dlm. BPFK/02/5/1.3*** *Label Amaran Tentang Penggunaan Bahan Chelidonium majus*
42.	**CHITOSAN** The following statement shall be included on the labels and package inserts of products containing chitosan. **"DERIVED FROM SEAFOOD"** **Reference:** ***Bil. (52) dlm. BPFK/02/5/1.3*** *Muatkan Kenyataan 'Derived From Seafood' Pada Label Produk Jika Bahan Aktif Adalah Dari Sumber Laut*
43.	**CHLORHEXIDINE** The following statements shall be included in the package insert, label and RiMUP of pharmaceutical products containing Chlorhexidine: **Package Insert** **a) Warnings and Precautions:** [Product Name] contains chlorhexidine. Chlorhexidine is known to induce hypersensitivity, including generalised allergic reactions and anaphylactic shock. The prevalence of chlorhexidine hypersensitivity is unknown, but available literature suggests this is likely to be very rare. [Product Name] should not be administered to anyone with a possible history of an allergic reaction to chlorhexidine. If any signs or symptoms of a suspected hypersensitivity reaction such as itching, skin rash, redness, swelling, breathing difficulties, light headedness, and rapid heart rate develop, immediately stop using the product. Appropriate therapeutic countermeasures must be instituted as clinically indicated.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	b) Adverse Effects/ Undesirable Effects: Immune system disorders Frequency not known: Hypersensitivity including anaphylactic shock **Label and Consumer Medication Information Leaflet (RiMUP)** [Product Name] contains chlorhexidine. Inform your healthcare provider if you have a known allergy to chlorhexidine. Stop using this product and seek immediate medical assistance if you experience rash, itching, swelling, breathing difficulties, light-headedness or rapid heartbeat. **Reference: Directive No. 8, 2017.** ***BPFK/PPP/07/25 (13) Jld. 1*** *Direktif Untuk Semua Produk Farmaseutikal Yang Mengandungi Chlorhexidine: Pengemaskinian Sisip Bungkusan, Label dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Reaksi Hipersensitiviti*
44.	**CHLORPHENIRAMINE** The following statement shall be included on the labels and package inserts of liquid oral products containing Chlorpheniramine: **WARNING** When used for treatment of cough and cold; (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. **Reference:** ***Bil. (34) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*
45.	**CHORIONIC GONADOTROPHIN** The following statement shall be included in the package inserts of products containing Chorionic gonadotrophin: **The ovulation cycle should be monitored with oestriol levels and ultrasonography**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
46.	**CLEMASTINE** The following statement shall be included on the labels and package inserts of liquid oral products containing Clemastine: **WARNING** When used for treatment of cough and cold: (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. **Reference:** ***Bil. (34) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*
47.	**CLARITHROMYCIN** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing Clarithromycin: **Package Insert** **a) Warnings and Precautions:** In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCARs) [e.g. Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP)], [product name] should be discontinued immediately and appropriate treatment should be urgently initiated. **b) Adverse Effects/ Undesirable Effects:** Skin and Subcutaneous Tissue Disorders Frequency not known: severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP). **c) Contraindications:** Concomitant administration of Clarithromycin and the following drugs is contraindicated: Domperidone as this may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, and torsades de pointes (See Section Interactions).

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	d) Interactions: Co-administration of Clarithromycin, known to inhibit CYP3A, and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant drug. The following drugs or drug classes are known or suspected to be metabolized by CYP3A isozyme: Domperidone **Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects:** [Product name] may cause severe allergy and serious skin reactions. Stop using [Product name] and seek medical assistance immediately if you experience any of the following symptoms: • skin reddening, blisters, rash, fever, sore throat or eye irritation **b) Before you use [Product name]:** Do not take [product name] if you are taking any of the following medicines: domperidone (used for nausea & vomiting) **References:** ***Directive No. 22, 2018.*** *BPFK/PPP/07/25 (22) Jld.2 Direktif Untuk Semua Produk Yang Mengandungi Azithromycin, Clarithromycin, Erythromycin dan Roxithromycin: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Severe Cutaneous Adverse Reactions (SCARs)* ***Directive No. 32, 2018.*** *BPFK/PPP/07/25 (32) Jld. 2 Direktif Untuk Semua Produk Yang Mengandungi Clarithromycin: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Interaksi Ubat Yang Mengakibatkan Peningkatan Risiko QT Interval Prolongation*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
48.	**CLINDAMYCIN** The package insert must emphasize the possibility of pseudomembranous colitis with the use of the drug. The package insert must include the **following boxed or emphasized statements/ warning:** • Clindamycin therapy has been associated with severe colitis which may end fatally. • It should be reserved for serious infections where less toxic antimicrobial agents are inappropriate. • It should not be used in patients with nonbacterial infections, such as most upper respiratory tract infections. • Its use in newborns is contraindicated.
49.	**CLOPIDOGREL** The following statement shall be included in the package inserts of products containing Clopidogrel: **WARNINGS AND PRECAUTIONS** Pharmacogenetics: Based on literature data, patients with genetically reduced CYP22C19 function (intermediate or poor metabolisers) have lower systemic exposure to the active metabolite of clopidogrel and diminished antiplatelet responses, and generally exhibit higher cardiovascular event rates following myocardial infarction than do patients with normal CYP2C19 function. **INTERACTION** Since clopidogrel is metabolised to its active metabolite by CYP2C19, use of drugs that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in clinical efficacy. Concomitant use of drugs that inhibit CYP2C19 (e.g proton pump inhibitors) should be discouraged. **PHARMACOKINETIC PROPERTIES** The oxidative step is regulated primarily by Cytochrome P450 ISOENZYMES 2B6, 3A4, 1A1, 1A2 and 2C19. **Reference:** ***Bil (42) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Berkaitan Dengan "Possible Interaction Between Clopidogrel and Proton Pump Inhibitors" yang Perlu Dimuatkan Pada Sisip Bungkusan Produk Clopidogrel*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
50.	**CLOZAPINE** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing Clozapine; **Package Insert** **a) Contraindications** Paralytic ileus **b) Warnings and Precautions** Clozapine exerts anticholinergic activity, which may produce undesirable effect throughout the body. Probably on account of its anticholinergic properties, [product name] has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, fecal impaction, paralytic ileus, megacolon and intestinal infarction/ischaemia. On rare occations these cases have proved fatal. Careful monitoring during treatment with [product name] to identify early, the onset of constipation, followed by effective management of constipation are recommended to prevent complications. **c) Adverse Effects/ Undesirable Effects:** Gastrointestinal disorders: (very rare) intestinal obstruction, ileus, faecal impaction Post-marketing: megacolon*, intestinal infarction/ischaemia*, intestinal necrosis*, intestinal ulceration*, intestinal perforation*, colitis (*These adverse drug reactions were sometimes fatal) **d) Interactions** Due to the possibility of additive effects, caution is essential when substances possessing anticholinergic effects are given concomitantly with [product name]. **Consumer Medication Information Leaflet (RiMUP)** **a) When you must not use it:** Do not take [product name] if you suffer or have ever suffered from severe constipation, obstruction of the bowel or any other condition which has affected your large bowel.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	b) Taking other medicines: Tell your doctor or pharmacist if you are taking or have recently taken medicines which cause constipation (such as anticholinergic, which are used to relieve stomach cramps, spasms and travel sickness). **c) While you are using [product name]:** Tell your doctor or pharmacist if you have experienced constipation, abdominal pain, abdominal tenderness, fever, bloating and/or bloody diarrhea. Your doctor will need to examine you. **d) Side effects:** Abdominal pain, cramping, swollen abdomen, vomiting, constipation and failure to pass gas which may be signs and symptoms of bowel obstruction. **Reference: Directive No. 3, 2021.** ***NPRA.600-1/9/13 (13)*** *Direktif Untuk Semua Produk Yang Mengandungi Clozapine: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Komplikasi Usus Yang Serius Akibat Sembelit*
51.	**COBICISTAT** The following statements shall be <u>included in the package insert</u> and <u>Consumer Medication Information Leaflet (RiMUP)</u> of products containing Cobicistat: **<u>Package Insert</u>** **a) Interactions:**

Medicinal product by therapeutic areas	***Effects on medicinal product levels.***	***Recommendation concerning co-administration with [product name]***
All corticosteroids excluding cutaneous products		

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Corticosteroids primarily metabolised by CYP3A (including betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone). | *Interaction not studied with any of the components of [product name].* *Plasma concentrations of these medicinal products may be increased when co-administered with [product name], resulting in reduced serum cortisol concentrations.* | *Concomitant use of [product name] and corticosteroids that are metabolised by CYP3A (e.g. fluticasone propionate or other inhaled or nasal corticosteroids) may increase the risk of development of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression.* *Co-administration with CYP3A-metabolised corticosteroids is not recommended unless the potential benefit to the patient outweighs the risk, in which case patients should be monitored for systemic corticosteroid effects. Alternative corticosteroids which are less dependent on CYP3A metabolism e.g. beclomethasone for intranasal or inhalational use should be considered, particularly for long-term use.*
	Consumer Medication Information Leaflet (RiMUP) **a) Before you use [product name]:** It is important to tell your doctor if you are taking corticosteroids such as betamethasone, budesonide, fluticasone, mometasone, prednisone and triamcinolone. These medicines are used to treat allergies, asthma, inflammatory bowel diseases, inflammatory conditions of the eyes, joints and muscles and other inflammatory conditions. If alternatives cannot be used, its use should only take place after medical evaluation and under close monitoring by your doctor for corticosteroid side effects. **Reference: Directive No. 2, 2018**. ***BPFK/PPP/07/25 (2) Jld. 2*** *Direktif Untuk Semua Produk Yang Mengandungi Cobicistat dan Kortikosteroid (Kecuali Produk Untuk Kegunaan Luar): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Interaksi Ubat*
52.	**CODEINE** The following safety information/ statements shall be included in the package inserts of products containing Codeine: **Indications** [Product name] is indicated for the relief of painful disorders such as headache, dysmenorrhea, conditions involving musculoskeletal pain, myalgias and neuralgias. It is also indicated as an analgesic and antipyretic in conditions accompanied by discomfort and fever, such as the common cold and viral infections. [Product name] is an effective analgesic after dental work and tooth extractions.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Codeine is indicated in patients older than 12 years of age for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen (alone). **Dosing and Administrations** Paediatric population: • Children aged less than 12 years: Codeine should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine. [Product name] is contraindicated in children below the age of 12 years for the symptomatic treatment of cold. • Children aged 12 years to 18 years: [Product name] is not recommended for use in children aged 12 years to 18 years with compromised respiratory function. **Contraindications** • In children below the age of 12 years for the symptomatic treatment of colds due to an increased risk of developing serious and life-threatening adverse reactions. • In all paediatric patients (0-18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to increased risk of developing serious and life-threatening adverse reactions. • In women who are breastfeeding. • In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers. **Warnings and Precautions** CYP2D6 metabolism Codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect will not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an extensive or ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels. General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life-threatening and very rarely fatal. Estimates of prevalence of ultra-rapid metabolisers in different populations are summarised below:

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

Population	Prevalence %
African/Ethiopian	29%
African American	3.4 to 6.5%
Asian	1.2 to 2.0%
Caucasian	3.6 to 6.5%
Greek	6.0%
Hungarian	1.9%
Northern European	1.0 to 2.0%

Post-operative use in children

There have been reports in the published literature that codeine given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life-threatening adverse events including death. All children received doses of codeine that were within the appropriate dose range; however, there was evidence that these children were either ultra-rapid or extensive metabolisers in their ability to metabolise codeine to morphine.

Children with compromised respiratory function

Codeine is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity.

Pregnancy and Lactation

Pregnancy

Careful consideration should be given before prescribing the product for pregnant patients. Opioid analgesics may depress neonatal respiration and cause withdrawal effects in neonates of dependent mothers.

As a precautionary measure, use of [Product name] should be avoided during the third trimester of pregnancy and during labor.

Breastfeeding

[Product name] is contraindicated in women during breastfeeding.

At normal therapeutic doses codeine and its active metabolite may be present in breast milk at very low doses and is unlikely to adversely affect the breast fed infant. However, if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolite, morphine, may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant, which may be fatal.

Reference: Directive No. 16, 2016. *BPFK/PPP/07/25 (2) Jld. 1 Direktif Bagi Semua Produk Yang Mengandungi Codeine Dengan Maklumat Keselamatan Berkaitan Risiko Kesan Advers Respiratory Depression*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
53.	**COLCHICINE** The following statement shall be included in the package inserts of products containing Colchicines: **INTERACTIONS** Potential risk of severe drug interactions, including death, in certain patients treated with colchicine and concomitant P-glycoprotein or strong CYP3A4 inhibitors such as clarithromycin, cyclosporin, erythromycin, calcium channel antagonists (e.g Verapamil and Diltiazem), telithromycin, ketoconazole, itraconazole, HIV protease inhibitors and nefazodone. P-Glycoprotein or strong CYP3A4 inhibitors are not to be used in patients with renal or hepatic impairment who are taking colchicine. A dose reduction or interruption of colchicine treatment should be considered in patients with normal renal and hepatic function if treatment with a P-glycoprotein or a strong CYP3A4 inhibitor is required. Avoid consuming grapefruit and grapefruit juice while using colchicine. **Reference:** ***Bil (45) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Berkaitan Dengan "Severe Drug Interaction Between Colchicine and P-Glycoprotein or Strong CYP3A4 Inhibitors" Yang Perlu Dimuatkan Pada Sisip Bungkusan Produk Colchicine*
54.	**CORTICOSTEROID** **54.1** The following statements shall be included in the package insert and RiMUP of inhaled corticosteriod used for treatment of Chronic Obstructive Pulmonary Disease (COPD) such as **budesonide** and **fluticasone** (product containing single active ingredient and in combination) and **beclomethasone** (only for combination product): **Package Insert** **a) Warnings and Precautions:** Pneumonia in patients with COPD An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively across all studies. There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Physicians should remain vigilant for the possible development of pneumonia in patient with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations. Risk factors for pneumonia in patients with COPD include current smoking status, older age, low body mass index (BMI) and severe COPD. **b) Adverse Effects / Undesirable Effects:** "Pneumonia (in COPD patients)" to be listed as "Common" adverse drug reaction in the "Infections and Infestations" SOC. **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Side Effects** <u>Pneumonia (infection of the lung) in COPD patients (common side effect)</u> • Tell your doctor if you have any of the following while taking [product name] they could be symptoms of a lung infection: - Fever or chills; - Increased mucus production or change in mucus colour; - Increased cough or increased breathing difficulties. **54.2** The following statements shall be <u>included in the package insert and RiMUP</u> of products containing corticosteroid (except products for external use): **(i) Products containing Beclomethasone:** **<u>Package Insert</u>** **a) Interactions with Other Medicaments:** Beclomethasone is less dependent on CYP3A metabolism than some other corticosteroids, and in general interactions are unlikely; however the possibility of systemic effects with concomitant use of strong CYP3A inhibitors (e.g. cobicistat) cannot be excluded, and therefore caution and appropriate monitoring is advised with the use of such agents. **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Before you use [product name]:** Some medicines may increase the effects of [product name] and your doctor may wish to monitor you carefully if you are taking these medicines (including some medicines for HIV such as cobicistat).

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	(ii) Products containing corticosteroids other than Beclomethasone: **Package Insert** **a) Interactions:** Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects. **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [product name]:** Some medicines may increase the effects of [product name] and your doctor may wish to monitor you carefully if you are taking these medicines (including some medicines for HIV such as cobicistat). **References:** **Directive No. 9, 2017.** ***BPFK/PPP/07/25 (14) Jld. 1*** *Direktif Untuk Semua Produk Inhalasi Kortikosteroid Yang Digunakan Untuk Rawatan Chronic Obstructive Pulmonary Disease (COPD): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Tambahan Berkenaan Peningkatan Risiko Pneumonia* **Directive No. 2, 2018.** ***BPFK/PPP/07/25 (2) Jld. 2*** *Direktif Untuk Semua Produk Yang Mengandungi Cobicistat dan Kortikosteroid (Kecuali Produk Untuk Kegunaan Luaran): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Interaksi Ubat*
55.	**COX-2 INHIBITORS** The following statement shall be included in the package insert of COX-2 Inhibitors products containing Celecoxib and Etoricoxib: • Contraindication for patients who have increased risk of cardiovascular disease (ischeamic heart disease and stroke). • Warning to prescriber when prescribing COX-2 Inhibitors to patients with risk factors of heart disease, hypertension (high blood pressure), hyperlipidemia, diabetes, smoking patient and patient with peripheral arterial disease. • Statement on limiting the period and dosing is written as 'Given the association between cardiovascular risk and exposure to COX-2 Inhibitors, doctors are advised to use the lowest effective dose for the shortest possible duration of treatment'. • Contraindication for patient using Etoricoxib is written as 'Contraindication for Etoricoxib in patients with hypertension (high blood pressure) whose blood pressure is not under control'. **Reference:** ***Bil. (46) dlm. BPFK/02/5/1.3*** *Keputusan Mesyuarat PBKD - Tindakan-tindakan Regulatori Terhadap COX-2 Inhibitors: Celecocib dan Etoricoxib*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
56.	**CYPROTERONE ACETATE** The following statement shall be included in the package inserts of products containing Cyproterone acetate: **WARNINGS AND PRECAUTIONS** Direct hepatic toxicity, including jaundice, hepatitis and hepatic failure, which has been fatal in some cases, has been reported in patients treated with 100mg or more of cyproterone acetate. Most reported cases are in men with prostatic cancer. Toxicity is dose-related and develops, usually, several months after treatment has begun. Liver function tests should be performed pre-treatment and whenever any symptoms or signs suggestive of hepatotoxicity occur. If hepatotoxicity is confirmed, cyproterone acetate should normally be withdrawn, unless the hepatotoxicity can be explained by another cause, e.g. metastatic disease, in which case cyproterone acetate should be continued only if the perceived benefit outweighs the risk.
57.	**CYPROTERONE ACETATE WITH ETHINYLESTRADIOL IN COMBINATION** **CYPROTERONE ACETATE 2MG AND ETHINYLESTRADIOL 0.035MG** The following statement shall be included in the package inserts of products containing Cyproterone acetate 2mg and Ethinylestradiol 0.035mg **INDICATIONS** - Treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhoea) and/or hirsutism in women of reproductive age. - For the treatment of acne, [product name] should only be used after topical therapy or systemic antibiotic treatments have failed. - Since [product name] is also a hormonal contraceptive, it should not be used in combination with other hormonal contraceptives. **DOSAGE AND METHOD OF ADMINISTRATION** (At the beginning part with **bold** formatting) **Note: [Product name] should not be prescribed for the purpose of contraception alone. However, when taken as recommended, [product name] will provide reliable contraception in patients treated for the above clinical conditions. If patient compliance is uncertain and contraception is necessary, then a supplementary non-hormonal contraceptive method should be considered.** **ADVERSE EFFECTS/ UNDESIRABLE EFFECTS:** - Vascular Disorders - Rare: Thromboembolism

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
58.	**CYTOTOXIC AGENT** The following boxed statement shall be included on the label of products containing Cytotoxic agents: **CAUTION : CYTOTOXIC AGENT** ***Note:*** *The label caution should be printed prominently on the label.*
59.	**DECITABINE** The following statements shall be included in the package insert for products containing decitabine; **Package Insert** **a) Warnings and Precautions:** Differentiation syndrome Cases of differentiation syndrome (also known as retinoic acid syndrome) have been reported in patients receiving decitabine. Differentiation syndrome may be fatal. Treatment with high dose IV corticosteroids and hemodynamic monitoring should be considered at first onset of symptoms or signs suggestive of differentiation syndrome. Temporary discontinuation should be considered until resolution of symptoms and if resumed, caution is advised. **b) Adverse Effects/ Undesirable Effects:** Neoplasms benign, malignant and unspecified (including cysts and polyps) Frequency 'Very rare': Differentiation syndrome **Reference: Directive No. 24, 2021.** ***NPRA.600-1/9/13 (34)*** *Direktif Untuk Semua Produk Yang Mengandungi Decitabine: Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Risiko Differentiation Syndrome*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
60.	**DEXBROMPHENIRAMINE** The following statement shall be included on the labels and package inserts of liquid oral products containing Dexbrompheniramine: **WARNING** When used for treatment of cough and cold: (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. **Reference:** ***Bil. (34) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*
61.	**DEXTROMETHORPHAN** The following statement shall be included on the labels and package inserts of liquid oral products containing Dextromethorphan: **WARNING** When used for treatment of cough and cold: (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. **Reference:** ***Bil. (34) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*
62.	**DICLOFENAC SODIUM** The following statement shall be included in the package inserts of products containing Diclofenac sodium: **WARNINGS AND PRECAUTIONS** Severe cutaneous reactions, including Stevens - Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome), have been reported with diclofenac sodium. Patients treated with diclofenac sodium should be closely monitored for signs of hypersensitivity reactions. Discontinue diclofenac sodium immediately if rash occurs. Adverse effects: Dermatological: Occasional - rashes or skin eruptions Cases of hair loss, bullous eruptions, erythema multiforme, Stevens- Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), and photosensitivity reactions have been reported.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
63.	**DICLOFENAC (SYSTEMIC FORMULATION)** The following statement shall be included in the package inserts of products containing Diclofenac: **DOSAGE AND ADMINISTRATION** **DOSAGE** As a general recommendation, the dose should be individually adjusted. Adverse effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see section WARNINGS AND PRECAUTIONS). **ESTABLISHED CARDIOVASCULAR DISEASE OR SIGNIFICANT CARDIOVASCULAR RISK FACTORS** Treatment with diclofenac is generally not recommended in patients with established cardiovascular disease (congestive heart failure, established ischemic heart disease, peripheral arterial disease) or uncontrolled hypertension. If needed, patients with established cardiovascular disease, uncontrolled hypertension, or significant risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes melilitus and smoking) should be treated with diclofenac only after careful consideration and only at doses ≤100 mg daily if treated for more than 4 weeks (see section WARNINGS AND PRECAUTIONS). **CONTRAINDICATIONS** Severe cardiac failure (see section WARNINGS AND PRECAUTIONS). **WARNINGS AND PRECAUTIONS** **Cardiovascular Effects** Treatment with NSAIDs including diclofenac, particularly at high dose and in long term, maybe associated with an increased risk of serious cardiovascular thrombotic events (including myocardial infarction and stroke). Treatment with diclofenac is generally not recommended in patients with established cardiovascular disease (congestive heart failure, established ischemic heart disease, peripheral arterial disease) or uncontrolled hypertension. If needed, patients with established cardiovascular disease, uncontrolled hypertension, or significant risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes melilitus and smoking) should be treated with diclofenac only after careful consideration and only at doses ≤100 mg daily when treatment continues for more than 4 weeks. As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the lowest effective daily dose should be used for the shortest duration possible. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially when treatment continues for more than 4 weeks.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Patients should remain alert for the signs and symptoms of serious arteriothrombotic events (e.g. chest pain, shortness of breath, weakness, slurring of speech), which can occur without warnings. Patients should be instructed to see a physician immediately in case of such an event. **ADVERSE EFFECTS / UNDESIRABLE EFFECTS** **Cardiac Disorders** Uncommon*: Myocardial infarction, cardiac failure, palpitations, chest pain. * The frequency reflects data from long-term treatment with a high dose (150 mg/day). **Description of Selected Adverse Drug Reactions** **Arteriothrombotic events** Meta-analysis and pharmacoepidemiological data point towards an increased risk of arteriothrombotic events (for example myocardial infarction) associated with the use of diclofenac, particularly at a high dose (150 mg daily) and during long-term treatment (see section WARNINGS AND PRECAUTIONS). **Reference: Directive No. 7, 2015.** ***Bil. (30)dlm. BPFK/PPP/07/25*** *Direktif Untuk Semua Produk Yang Mengandungi Diclofenac (Formulasi sistemik): Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Kesan Advers Kardiovaskular*
64.	**DICLOFENAC (ALL PRODUCTS EXCEPT PRODUCTS FOR CUTANEOUS USE)** The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing Diclofenac (except products for cutaneous use); **<u>Package Insert</u>** **a) Warnings & Precautions** <u>Gastrointestinal effects</u> NSAIDs, including diclofenac, may be associated with increased risk of gastrointestinal anastomotic leak. Close medical surveillance and caution are recommended when using diclofenac after gastrointestinal surgery. **b) Adverse Effects/Undesirable Effects:** <u>Cardiac disorders:</u> Kounis syndrome: Frequency “not known”

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Consumer Medication Information Leaflet (RiMUP) **a) Before you start to use it:** Tell your doctor if you recently had or you are going to have a surgery of the stomach or intestinal tract before receiving/taking/using [product name], as [product name] can sometimes worsen wound healing in your gut after surgery. **b) Side Effects:** Frequency "not known": Chest pain, which can be a sign of a potentially serious allergic reaction called Kounis syndrome. **Reference: Directive No. 4, 2020.** ***BPFK/PPP/07/25 (4) Jld. 4*** *Direktif Untuk Semua Produk Yang Mengandungi Diclofenac (Kecuali Sediaan Untuk Kegunaan Pada Kulit): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Penambahan Maklumat Keselamatan Berkaitan Risiko Anastomotic Leakage Dan Kounis Syndrome*
65.	**DICYCLOMINE** The following boxed warning shall be included on the labels and in the package inserts of products containing Dicyclomine: **WARNING** Dicyclomine is not recommended for use in infants under the age of six month
66.	**DIPHENHYDRAMINE** The following statement shall be included on the labels and in the package inserts of products containing Diphenhydramine: **WARNING** When used for treatment of cough and cold: (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. **Reference:** ***Bil. (34) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
67.	**DIPHENOXYLATE** 1. The following boxed warning shall be included on the labels of products containing Diphenoxylate: **NOT RECOMMENDED FOR CHILDREN UNDER 6 YEARS OF AGE.** 2. The following statement shall be included in the package insert of products containing Diphenoxylate: **WARNING** **Not recommended for children under 6 years of age.** **PRECAUTION** Appropriate fluid and electrolyte therapy should be given to protect against dehydration in all cases of diarrhoea. Oral rehydration therapy which is the use of appropriate fluids including oral rehydration salts remains the most effective treatment for dehydration due to diarrhoea. The intake of as much of these fluids as possible is therefore imperative. Drug-induced inhibition of peristalsis may result in fluid detention in the intestine, which may aggravate and mask dehydration and depletion of electrolytes, especially in young children. If severe dehydration of electrolyte imbalance is present, diphenoxylate should be withheld until appropriate corrective therapy has been initiated.
68.	**DOMPERIDONE** The following statement shall be included on the package inserts and RiMUP of products containing Domperidone: **Package insert** **INDICATIONS** Domperidone is indicated for the relief of the symptoms of nausea and vomiting. This includes: • Nausea and vomiting of functional, organic, infectious or dietary origin. • Nausea and vomiting induced by: - radiotherapy or drug therapy.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

- dopamine agonists (such as L-dopa and bromocriptine) used in the treatment of Parkinson's disease.

DOSAGE AND ADMINISTRATION

It is recommended to take [product name] 15-30 minutes before meals. If taken after meals, absorption of the drug is somewhat delayed.

Adults and adolescents ≥ 12 years of age and weighing ≥35 kg & children <12 years of age and weighing ≥ 35 kg

The dose of [product name] should be the lowest effective dose for the individual situation (typically 30 mg/day) and can be increased if necessary to a maximum daily oral dose of 40 mg.
Usually, the maximum treatment duration should not exceed one week for the treatment of acute nausea and vomiting. If nausea and vomiting persists for longer than one week, patients should consult their physician. For other indications, the initial duration of treatment is up to four weeks. If treatment exceeds four weeks, patients should be re-evaluated and the need for continued treatment reassessed.

Formulation (domperidone per unit)	**Dosage**	**Maximum dose per day**
Tablets (10 mg/tablet)	1 tablet three to four times per day	40 mg (4×10 mg tablet).
Oral suspension (1 mg/ml)	10 mL three to four times per day	40 mg (40 mL of 1 mg/mL oral suspension)

Adults and adolescents (≥ 12 years of age) weighing < 35 kg

The dose of [product name] should be the lowest effective dose. The total daily dose is dependent on weight (see table below).

Usually, the maximum treatment duration should not exceed one week for the treatment of acute nausea and vomiting. For other indications, the initial duration of treatment is up to four weeks. If treatment exceeds four weeks, patients should be reevaluated and the need for continued treatment reassessed. Due to the need for accurate dosing, tablets are unsuitable for use in adults and adolescents weighing less than 35 kg.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

Formulation (domperidone per unit)	Dosage	Maximum dose per day
Oral suspension (1 mg/mL)	0.25 mg/kg three to four times per day	1 mg/kg but no more than 35 mL (35mg)

Infants and children < 12 years of age and weighing < 35 kg

The efficacy of [product name] has not been established in infants and children < 12 years of age and weighing < 35 kg.

Renal impairment

Since the elimination half-life of domperidone is prolonged in severe renal impairment (serum creatinine > 6 mg/100 mL, i.e. > 0.6 mmol/L), the dosing frequency of [product name] should be reduced to once or twice daily, depending on the severity of the impairment, and the dose may need to be reduced. Patients with severe renal impairment should be reviewed regularly.

Hepatic impairment

[Product name] is contraindicated for patients with moderate (Child-Pugh 7 to 9) or severe (Child-Pugh >9) hepatic impairment. Dose adjustment is not required for patients with mild (Child-Pugh 5 to 6) hepatic impairment.

CONTRAINDICATIONS

[Product name] is contraindicated in the following situations:

- Known hypersensitivity to domperidone or any of the excipients.
- Prolactin-releasing pituitary tumour (prolactinoma).
- In patients who have known existing prolongation of cardiac conduction intervals, particularly QTc, patients with significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure (see Warnings and Precautions).
- co-administration with QT-prolonging drugs
- co-administration with potent CYP3A4 inhibitors regardless of their QT-prolonging effects (See Section Interactions).
- Whenever stimulation of gastric motility might be dangerous, e.g., in the presence of gastro-intestinal haemorrhage, mechanical obstruction or perforation.
- In patients with moderate or severe hepatic impairment).

INTERACTIONS

The main metabolic pathway of domperidone is through CYP3A4. In vitro and human data show that the concomitant use of drugs that significantly inhibit this enzyme

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	may result in increased plasma levels of domperidone. Co-administration of domperidone with potent CYP3A4 inhibitors which have been shown to cause QT interval prolongation is contraindicated (See Section Contraindications). **WARNINGS AND PRECAUTIONS** **Cardiovascular effects** Domperidone has been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT-prolongation and torsades de pointes in patients taking domperidone. These reports included patients with confounding risk factors, electrolyte abnormalities and concomitant treatment which may have been contributing factors (see Adverse Reactions). Epidemiological studies showed that domperidone was associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death (see Adverse Reactions). A higher risk was observed in patients older than 60 years, patients taking daily doses greater than 30 mg, and patients concurrently taking QT-prolonging drugs or CYP3A4 inhibitors. Domperidone should be used at the lowest effective dose in adults and children. Domperidone is contraindicated in patients with known existing prolongation of cardiac conduction intervals, particularly QTc, in patients with significant electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia), or bradycardia, or in patients with underlying cardiac diseases such as congestive heart failure due to increased risk of ventricular arrhythmia (see Contraindications). Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) or bradycardia are known to be conditions increasing the proarrythmic risk. Treatment with domperidone should be stopped if signs or symptoms occur that may be associated with cardiac arrhythmia, and the patients should consult their physician. Patients should be advised to promptly report any cardiac symptoms. **ADVERSE EFFECTS / UNDESIRABLE EFFECTS** {information to be included} **Postmarketing:** **Cardiac Disorders** Frequency: Very rare Ventricular arrhythmias, QTc prolongation, Torsade de Pointes, Sudden cardiac death (see Warnings and Precautions)

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Consumer Medication Information Leaflet (RiMUP) **a) Before you use [Product name]:** Do not take [product name] if you are taking any of the following medicines: clarithromycin (antibiotic) **b) How to use [product name]:** You should always take the lowest amount of [product name] that works for you and you should not take it for longer than is necessary. Although the amount of [product name] you should usually take is described below, your doctor may adjust your dose to your personal needs. [Product name] is most effective if taken 15-30 minutes before meals. Adults and adolescents (12 years of age and over) weighing 35 kg or more; children weighing 35kg or more: Tablets: Take 1 tablet 3 to 4 times a day. Do not take more than 4 tablets per day (40 mg/day). Oral suspension: Take 10mL of oral suspension 3 or 4 times a day. Do not take more than 40mL per day (40 mg/day). Adults and adolescents weighing less than 35 kg: Oral suspension: Give 0.25 milliliters of the oral suspension per kilogram of body weight 3 or 4 times a day. The maximum dose per day is 1 mg/kg but do not exceed 35 mg per day. Infants and children less than 12 years of age and weighing less than 35kg: The effectiveness of [product name] has not been established in infants and children under 12 years of age with a body weight of <35 kg. **References:** **Directive No. 4, 2015.** ***Bil. (28) dlm. BPFK/PPP/07/25*** *Direktif Untuk Semua Produk Domperidone Untuk Mengehadkan Penggunaan Berikutan Risiko Kesan Advers Jantung* **Directive No. 31, 2018.** ***BPFK/PPP/07/25 (31) Jld. 2*** *Direktif Untuk Semua Produk Yang Mengandungi Domperidone: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Interaksi Ubat Yang Mengakibatkan Peningkatan Risiko QT Interval Prolongation* **Directive No. 6, 2020.** ***BPFK/PPP/07/25 (6) Jld. 4*** *Direktif Untuk Semua Produk Yang Mengandungi Domperidone: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Penggunaan Dalam Kalangan Golongan Pediatrik*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
69.	**DOPAMINERGIC INGREDIENT** The following warning/ statement related to "Sudden sleep onset" shall be included in the package insert and product literature of products containing dopaminergic ingredients **WARNINGS AND PRECAUTIONS** ……. has been associated with somnolence and episodes of sudden onset, particularly in patients with Parkinson's diseases. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported very rarely. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with ……. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore, a reduction of dosage or termination of therapy may be considered. **EFFECTS ON ABILITY TO DRIVE AND USE MACHINES** Patients being treated with ……. and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved (see also section on warnings and precautions). **ADVERSE EFFECTS / UNDESIRABLE EFFECTS** ……. is associated with somnolence and has been associated very rarely with excessive daytime somnolence and sudden sleep onset episodes. **Reference:** ***Bil. 14 dlm. BPFK/02/5/1.3*** *Keputusan Mesyuarat PBKD - Keluaran Yang Mengandungi Bahan Aktif Dopaminergik: Tambahan Amaran Berkaitan Dengan 'Sudden Sleep Onset'*
70.	**DOXYCYCLINE** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing Doxycycline; **Package Insert** **a) Warnings and Precautions:** Some patients with spirochete infections may experience a Jarisch-Herxheimer reaction shortly after doxycycline treatment is started. Patients should be reassured that this is a usually self-limiting consequence of antibiotic treatment of spirochete infections. **b) Adverse Effects/Undesirable Effects:**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Immune system disorders Frequency not known: Jarisch-Herxheimer reaction (see Section Warnings and Precautions) **Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects:** [Product name] may cause Jarisch-Herxheimer reaction which usually consists of fever, chills, headache, muscle pain, and skin rash. The reaction occurs shortly after starting [product name] for spirochete infections and is often self-limiting. **Reference: Directive No. 19, 2018.** ***BPFK/PPP/07/25 (19) Jld. 2*** *Direktif Untuk Semua Produk Yang Mengandungi Doxycycline: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Jarisch-Herxheimer Reaction*
71.	**EFAVIRENZ** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing Efavirenz: **Package Insert** **a) Warnings and Precautions:** - QTc prolongation has been observed with the use of efavirenz (see Section Pharmacodynamics and Section Interaction with Other Medicaments). Consider alternatives to [Product name] when coadministered with a drug with a known risk of Torsade de Pointes or when administered to patients at higher risk of Torsade de Pointes. - Nervous System Symptoms: Late-onset neurotoxicity, including ataxia and encephalopathy (impaired consciousness, confusion, psychomotor slowing, psychosis, delirium), may occur months to years after beginning efavirenz therapy. Some events of late-onset neurotoxicity have occurred in patients with CYP2B6 genetic polymorphisms, which are associated with increased efavirenz levels despite standard dosing of [product name]. Patients presenting with signs and symptoms of serious neurologic adverse experiences should be evaluated promptly to assess the possibility that these events may be related to efavirenz use, and whether discontinuation of [product name] is warranted. **b) Pharmacodynamics:**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Cardiac Electrophysiology The effect of [Product name] on the QTc interval was evaluated in an open-label, positive and placebo controlled, fixed single sequence 3-period, 3-treatment crossover QT study in 58 healthy subjects enriched for CYP2B6 polymorphisms. The mean Cmax of efavirenz in subjects with CYP2B6 *6/*6 genotype following the administration of 600 mg daily dose for 14 days was 2.25-fold the mean Cmax observed in subjects with CYP2B6 *1/*1 genotype. A positive relationship between efavirenz concentration and QTc prolongation was observed. Based on the concentration-QTc relationship, the mean QTc prolongation and its upper bound 90% confidence interval are 8.7 ms and 11.3 ms in subjects with CYP2B6*6/*6 genotype following the administration of 600 mg daily dose for 14 days. (see Section Warnings and Precautions & Section Interaction with Other Medicaments). **c) Interactions:** QT Prolonging Drugs There is limited information available on the potential for a pharmacodynamic interaction between [Product name] and drugs that prolong the QTc interval. QTc prolongation has been observed with the use of efavirenz (see Section Pharmacodynamics and Section Warnings and Precautions). Consider alternatives to [Product name] when coadministered with a drug with a known risk of Torsade de Pointes. **d) Adverse Effects/ Undesirable Effects:** Postmarketing experiences: encephalopathy **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Before You Use [product name]:** Before you start to use it: Tell your doctor if you have any heart disorder. **b) Side effects:** Some nervous system symptoms [e.g. confusion, slow thoughts and physical movement and delusions (false beliefs) or hallucinations (seeing or hearing things that others do not see or hear)] may occur months to years after beginning [product name] therapy. Always notify your doctor or pharmacist if you have these symptoms or any side effects while taking [product name].

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	References: **Directive No. 18, 2018.** ***BPFK/PPP/07/25 (18) Jld. 2*** *Direktif Untuk Semua Produk Yang Mengandungi Efavirenz: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan QTc Prolongation* **Directive No. 4, 2021.** ***NPRA.600-1/9/13 (14)*** *Direktif Untuk Semua Produk Yang Mengandungi Efavirenz (Termasuk Produk Kombinasi): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Late Onset Neurotoxicity*
72.	**EPHEDRINE** The following statement shall be included on the labels and in the package inserts of products containing Ephedrine: **WARNING** When used for treatment of cough and cold: (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. **Reference:** ***Bil. (34) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*
73.	**ERYTHROMYCIN** 1. The following statement shall be included in the package insert and RiMUP of products containing erythromycin; **Package Insert** **a) Warnings and Precautions:** In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCARs) [e.g. Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP)], [product name] should be discontinued immediately and appropriate treatment should be urgently initiated. **b) Adverse Effects/Undesirable Effects:** Skin and Subcutaneous Tissue Disorders Frequency not known: severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP).

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Consumer Medication Information Leaflet (RiMUP) **Side Effects** [Product name] may cause severe allergy and serious skin reactions. Stop using [Product name] and seek medical assistance immediately if you experience any of the following symptoms: • skin reddening, blisters, rash, fever, sore throat or eye irritation **Reference: Directive Bil 22, 2018.** *Bil. (22) dlm BPFK/PPP/07/25 Jld.2 Direktif Untuk Semua Produk Yang Mengandungi Azithromycin, Clarithromycin, Erythromycin dan Roxithromycin: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Severe Cutaneous Adverse Reactions (SCARs)* 2. The following statement shall be included in the package insert and RiMUP of products containing erythromycin (except topical/ external and ophtalmic preparations); **Package Insert** **a) Warnings and Precautions:** There have been reports of infantile hypertrophic pyloric stenosis (IHPS) occurring in infants following erythromycin therapy. In one cohort of 157 newborns who were given erythromycin for pertussis prophylaxis, seven neonates (5%) developed symptoms of non-bilious vomiting or irritability with feeding and were subsequently diagnosed as having IHPS requiring surgical pyloromyotomy. Since erythromycin may be used in the treatment of conditions in infants which are associated with significant mortality or morbidity (such as pertussis or chlamydia), the benefit of erythromycin therapy needs to be weighed against the potential risk of developing IHPS. Parents and caregivers should be informed to contact their physician if vomiting and/ or irritability with feeding occurs. **b) Adverse Effects/Undesirable Effects:** Postmarketing Experience: Gastrointestinal Disorders: infantile hypertrophic pyloric stenosis. **Consumer Medication Information Leaflet (RiMUP)** **Side Effects** If you notice that the child vomits and/or irritability with feeding occurs, contact doctor immediately as it may be due to the Infantile Hypertrophic Pyloric Stenosis (IHPS).

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Reference: Directive No. 28, 2017. ***BPFK/PPP/07/25 (33) Jld. 1*** *Direktif Untuk Semua Produk Yang Mengandungi Bahan Aktif Azithromycin dan Erythromycin Kecuali Persediaan Topikal/ Eksternal dan Ubat Untuk Kegunaan Mata: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Amaran Berkaitan Risiko Infantile Hypertrophic Pyloric Stenosis (IHPS)*
74.	**ETHINYLESTRADIOL** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing ethinylestradiol; **Package Insert** **a) Contraindications:** [Product name] is contraindicated for concomitant use with the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir (See Section Warnings and Precautions and Section Interactions with Other Medicaments). **b) Warnings and Precautions:** ALT elevations During clinical trials with patients treated for hepatitis C virus infections (HCV) with the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir with/without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequent in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs). Patients who are taking ethinylestradiol-containing medicinal products must switch to an alternative method of contraception (e.g. progestin only contraception or non-hormonal methods) prior to initiating ombitasvir / paritaprevir/ ritonavir and dasabuvir therapy (See Section Contraindications and Section Interactions with Other Medicaments). **c) Interactions:** Concomitant use with the medicinal products containing ombitasvir/ paritaprevir/ ritonavir and dasabuvir, with or without ribavirin may increase the risk of ALT elevations (See Section Contraindications and Section Warnings and Precautions). Therefore, users must switch to an alternative method of contraception (e.g., progestogen-only contraception or non-hormonal methods) prior to starting therapy with this combination drug regimen. [Product name] can be restarted 2 weeks following completion of treatment with this combination drug regimen.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Consumer Medication Information Leaflet (RiMUP) **a) Before You Use [product name]:** When you must not use it: Do not use [product name] if you have Hepatitis C and are taking the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir. Taking other medicines: Do not use [product name] if you have Hepatitis C and are taking the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir. Your doctor will prescribe another type of contraceptive before starting the treatment with these medicinal products. **Reference: Directive No. 13, 2018**. ***BPFK/PPP/07/25 (13) Jld. 2*** *Direktif Untuk Semua Produk Yang Mengandungi Ethinylestradiol: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Risiko Peningkatan Paras Alanine Transaminase (ALT) Akibat Interaksi Dengan Produk Kombinasi Ombitasvir / Paritaprevir / Ritonavir dan Dasabuvir*
75.	**ETORICOXIB** The following statements shall be included in the package insert and RiMUP of pharmaceutical products containing Etoricoxib: **Package Insert** **Dosage and Administration:** Rheumatoid arthritis The recommended dose is 60 mg once daily. In some patients with insufficient relief from symptoms, an increased dose of 90 mg once daily may increase efficacy. Once the patient is clinically stabilised, down-titration to a 60 mg once daily dose may be appropriate. In the absence of an increase in therapeutic benefit, other therapeutic options should be considered. Ankylosing spondylitis The recommended dose is 60 mg once daily. In some patients with insufficient relief from symptoms, an increased dose of 90 mg once daily may increase efficacy. Once the patient is clinically stabilised, down-titration to a 60 mg once daily dose may be appropriate. In the absence of an increase in therapeutic benefit, other therapeutic options should be considered. **Consumer Medication Information Leaflet (RiMUP)** **How Much to Use:**

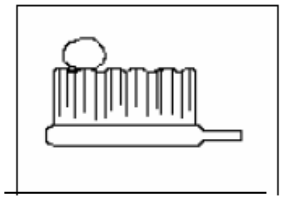
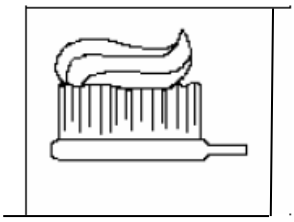
NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Rheumatoid arthritis The recommended dose is 60 mg once a day, and may increase to 90 mg once a day if needed. Ankylosing spondylitis The recommended dose is 60 mg once a day, and may increase to 90 mg once a day if needed. **Reference: Directive No. 13, 2017.** ***BPFK/PPP/07/25 (18) Jld. 1*** *Direktif Untuk Semua Produk Farmaseutikal Yang Mengandungi Etoricoxib: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Perubahan Dos Permulaan Bagi Rawatan Rheumatoid Arthritis dan Ankylosing Spondylitis*
76.	**FAMOTIDINE** The following statement shall be included in the package inserts of products containing Famotidine: **DOSAGE** Dosage adjustment is required for patients with moderate to severe renal insufficiency. Since CNS adverse effects have been reported in patients with moderate to severe renal insufficiency, to avoid excess accumulation of the drug, the dose of famotidine may be reduced to half the recommended dose or the dosing interval may be prolonged to 36 - 48 hours as indicated by the patient's clinical response. **WARNINGS AND PRECAUTIONS** As elderly patients are more likely to have decreased clearance of famotidine, care should be taken in dose selection and it may be useful to monitor renal function.
77.	**FIBRATES** The following statement shall be included in the package inserts of products containing Fibrates: **INTERACTION** Concurrent use of fibrates with HMG-CoA reductase inhibitors may cause severe myositis and myoglobinuria.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
78.	**FILGRASTIM** The following statement shall be included in the package inserts of ALL biosimilar products containing FILGRASTIM **WARNINGS AND PRECAUTIONS** Capillary leak syndrome has been reported after granulocyte-colony stimulating factor administration and is characterised by hypotension, hypoalbuminaemia, oedema and hemoconcentration. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care. Aortitis has been reported after G-CSF administration in healthy subjects and in cancer patients. The symptoms experienced included fever, abdominal pain, malaise, back pain and increased inflammatory markers (e.g. C-reactive protein and white blood cell count). In most cases aortitis was diagnosed by CT scan and generally resolved after withdrawal of G-CSF. **ADVERSE EFFECTS/ UNDESIRABLE EFFECTS** Clinical Trials **In Cancer Patients** Capillary Leak Syndrome, which can be life-threatening if treatment is delayed, has been reported uncommonly (≥1/1000 to < 1/100) in cancer patients undergoing chemotherapy following administration of granulocyte colony stimulating factors. **In Normal Donors undergoing peripheral blood progenitor cell mobilization** Capillary Leak Syndrome, which can be life-threatening if treatment is delayed, has been reported in healthy donors undergoing peripheral blood progenitor cell mobilization following administration of granulocyte colony stimulating factors. Post Marketing **Vascular disorders** Cases of capillary leak syndrome have been reported in the post marketing setting with granulocyte colony stimulating factor use. These have generally occurred in patients with advanced malignant diseases, sepsis, taking multiple chemotherapy medications or undergoing apheresis. Frequency "rare": Aortitis **References:** **Directive No. 13, 2014.** ***Bil. (20) dlm. BPFK/PPP/07/25*** *Direktif Untuk Semua Produk Yang Mengandungi Filgrastim dan Pegfilgrastim: Amaran Berkaitan Risiko Capillary Leak Syndrome (CLS) Bagi Pesakit Kanser dan Healthy Donor (Filgrastim) dan Bagi Pesakit Kanser (Pegfilgrastim)* **Directive No. 30, 2018.** ***Bil. (30) dlm. BPFK/PPP/07/25*** *Direktif Untuk Semua Produk Yang Mengandungi Filgrastim, Pegfilgrastim dan Lenograstim: Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Aortitis*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
79.	**FLUCLOXACILLIN** The following warning shall be included in the package insert of products containing Flucloxacillin: **WARNING** Liver Toxicity Flucloxacillin can cause severe hepatitis and cholestatic jaundice, which may be protracted. This reaction is more frequent in older patients and those who take the drug for prolonged periods (see Precaution, Adverse Reactions)

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
80.	**FLUCONAZOLE** The following statements shall be included in the package insert and RiMUP of pharmaceutical products containing Fluconazole: **Package Insert** **a) Pregnancy and Lactation:** Use During Pregnancy There have been reports of spontaneous abortion and congenital abnormalities in infants whose mothers were treated with 150mg of fluconazole as a single or repeated dose in the first trimester. Use in pregnancy should be avoided except in patients with severe or potentially life-threatening fungal infections in whom [product name] may be used if the anticipated benefit outweighs the possible risk to the fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be informed of the potential hazard to the fetus. Effective contraceptive measures should be considered in women of child-bearing potential and should continue throughout the treatment period and for approximately 1 week (5 to 6 half-lives) after the final dose. There have been reports of multiple congenital abnormalities in infants whose mothers were treated with high-dose (400mg/day to 800mg/day) fluconazole therapy for coccidioidomycosis (an unapproved indication). The relationship between fluconazole use and these events is unclear. Adverse fetal effects have been seen in animals only at high-dose levels associated with maternal toxicity. There were no fetal effects at 5 mg/kg or 10 mg/kg; increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 mg/kg and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg (approximately 20-60 times the recommended human dose) to 320 mg/kg, embryolethality in rats were increased and fetal abnormalities included wavy ribs, cleft palate and abnormal craniofacial ossification. Case reports describe a distinctive and a rare pattern of birth defects among infants whose mothers received high dose (400-800mg/day) fluconazole during most or all of the first trimester of pregnancy. The features seen in these infants include brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis, and congenital heart disease.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Use During Lactation Fluconazole is found in human breast milk at concentrations similar to plasma. Breast-feeding may be maintained after a single dose of 150mg fluconazole. Breast-feeding is not recommended after repeated use or after high-dose fluconazole. **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [product name]** Inform your doctor if you have such conditions: • Pregnant or planning to become pregnant [Product name] may cause harm to your unborn baby. You should not take [product name] while you are pregnant unless your doctor has told you to. Inform your doctor if you are pregnant or planning to become pregnant. If you are a woman of child-bearing potential, avoid becoming pregnant during treatment. Use effective contraception during treatment and for 1 week after treatment. • Breast-feeding [Product name] is excreted in human breast milk, hence its use in nursing mothers is not recommended.However, breast-feeding may be maintained if you took a single dose of [product name] 150mg. Breast-feeding is not recommended after a high dose (more than 150 mg) or repeated use of [product name]. **Reference: Directive No. 24, 2017.** ***BPFK/PPP/07/25 (29) Jld. 1*** *Direktif Untuk Semua Produk Yang Mengandungi Fluconazole: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Baharu Berkaitan Risiko Spontaneous Abortion Serta Memperkukuhkan Maklumat Keselamatan Berkaitan Multiple Congenital Abnormalities dan Penggunaan Dalam Kalangan Ibu Menyusu*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
81.	**FLUORIDE** All toothpastes containing Fluorides should be labeled with the following additional information: a. **DIRECTIONS ON USE** • Do not swallow – spit and rinse after use. b. **FOR CHILDREN BELOW 6 YEARS** • Use a pea-sized amount of toothpaste (less than 5mm). • Supervise child's brushing. c. **DIRECTIONS ON DENTAL HEALTH** • Brush at least twice a day. • Restrict the amount and frequency of sugary food. • Visit your dentist at least once a year. d. **GRAPHICS AS SHOWN** • *Child's use* • *Adult's use*  *Child's use*  *Adult's use*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
82.	**82.1. FLUOROQUINOLONE (ALL DOSAGE FORM)** The following statement shall be included in the package inserts of products containing Fluoroquinolone: **WARNINGS AND PRECAUTIONS** Exacerbation of myasthenia gravis Fluoroquinolones have neuromuscular blocking activity and may exacerbate muscle weakness in person with myasthenia gravis. Post marketing serious adverse events, including deaths and requirement for ventilator support have been associated with flouroquinolones use in persons with myasthenia gravis. Avoid flouroquinolones in patients with known history of myasthenia gravis **ADVERSE EFFECTS / UNDESIRABLE EFFECTS** Exacerbation of myasthenia gravis Post Marketing Experience **82.2. FLUOROQUINOLONE (SYSTEMIC FORMULATIONS INCLUDING ORAL AND INJECTION DOSAGE FORMS)** The following statement shall be included in the **package inserts**: **Package Insert** **a) Indication:** **(i) The following statement should be included:** Consideration should be given to official guidance on the appropriate use of antibacterial agents. **(ii) The following indication(s), if relevant, should be deleted:** • Acute bronchitis • Laryngitis • Pharyngitis-tonsillitis • Prophylaxis of infectious gastroenteritis / traveller's diarrhoea • Selective decontamination of gastrointestinal tract in patients with compromised immune system • Vaginal infections

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	(iii) The following indication(s), if relevant, should be restricted: • Acute bacterial rhinosinusitis* • Acute exacerbation of chronic obstructive pulmonary disease including chronic bronchitis* • Nosocomial pneumonia / Hospital-acquired pneumonia* • Acute otitis media* • External otitis* • Endocarditis* • Infection of cerebrospinal fluid* • Meningitis* • Septicaemia* • Uncomplicated acute cystitis / uncomplicated cystitis* • Prevention of exacerbations in women with recurring urinary tract infections* • Prevention of infection in surgical procedures in the urogenital system*,# • Pre-operative preparations for chronic cholesteatomatous otitis and chronic otitis spreading to bone* **(iv) The following text should be added after the restricted indications in part (iii):** *[Product name] should be only used : • When Pseudomonas is considered AND patient is allergic to antipseudomonal penicillins/cephalosporins; • For resistant organisms with no other alternative antibiotics available. #[Product name] should not be used >24 hours post operation. **b) Warnings and Precautions:** The use of [INN] should be avoided in patients who have experienced serious adverse reactions in the past when using fluoroquinolones containing products (see section Adverse Effects/Undesirable Effects). Treatment of these patients with [INN] should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Aortic aneurysm and dissection Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population. Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis). In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department. Prolonged, disabling and potentially irreversible serious adverse drug reactions Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving fluoroquinolones irrespective of their age and pre-existing risk factors. [INN] should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice. Tendinitis and tendon rupture Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in older patients (above 60 years of age), with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids*. Therefore, concomitant use of corticosteroids should be avoided. At the first sign of tendinitis (e.g. painful swelling, inflammation) the treatment with [INN] should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilisation). Corticosteroids should not be used if signs of tendinopathy occur. *[For systemically administered levofloxacin-containing products, the listing of risk factors should additionally include: "in patients receiving daily doses of 1000 mg levofloxacin".] Peripheral neuropathy Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with [INN] should be advised to inform their doctor and pharmacist prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop in order to prevent the development of potentially irreversible condition

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	(see section Adverse Effects/Undesirable Effects). **c) Adverse Effects/Undesirable Effects:** Musculoskeletal and connective tissue disorders* Nervous system disorders* General disorders and administrative site conditions* Psychiatric disorders* Eye disorders* Ear and labyrinth disorders* *Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendinitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of fluoroquinolones in some cases irrespective of pre-existing risk factors (see section Warnings and Precautions). The following statements shall be included in the **Consumer Medication Information Leaflet (RiMUP)**: **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [product name]:** Before you start to use it: - Tell your healthcare providers if you have been diagnosed with an enlargement or "bulge" of a large blood vessel (aortic aneurysm or large vessel peripheral aneurysm). - Tell your healthcare providers if you have experienced a previous episode of aortic dissection (a tear in the aorta wall). - Tell your healthcare providers if you have a family history of aortic aneurysm or aortic dissection or other risk factors or predisposing conditions (e.g. connective tissue disorders such as Marfan syndrome, or vascular Ehlers-Danlos syndrome, or vascular disorders such as Takayasu arteritis, giant cell arteritis, Behcet´s disease, high blood pressure, or known atherosclerosis). - You should not take fluoroquinolone antibacterial medicines, including [product name], if you have experienced any serious adverse reaction in the past when taking a fluoroquinolone (see section Things to be careful of and Side effects). In

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	this situation, you should inform your healthcare providers as soon as possible. **b) While you are using it:** Things to be careful of: If you feel sudden, severe pain in your abdomen, chest or back, go immediately to the emergency department. <u>Prolonged, disabling and potentially irreversible serious side effects</u> Fluoroquinolone antibacterial medicines, including [product name], have been associated with very rare but serious side effects, some of them being long lasting (continuing months or years), disabling or potentially irreversible. Stop taking your fluoroquinolone antibiotic and contact your healthcare providers immediately if you have the following signs of a side effect: • Tendon pain or swelling, often beginning in the ankle or calf. If this happens, rest the painful area until you can see your healthcare providers. • Pain in your joints or swelling in your shoulder, arms, or legs. • Abnormal pain or sensations (such as persistent pins and needles, tingling, tickling, numbness, or burning), weakness in your body, especially in the legs or arms, or difficulty walking. • Severe tiredness, depressed mood, anxiety, problems with your memory, or severe problems sleeping. • Changes in your vision, taste, smell, or hearing. Tell your healthcare providers if you have had one of the above effects during or shortly after taking a fluoroquinolone – this means you should avoid them in the future. You and your healthcare providers will decide on continuing the treatment considering also an antibiotic from another class. <u>Tendinitis and tendon rupture</u> Pain and swelling in the joints and inflammation or rupture of tendons may occur rarely. Your risk is increased if you are elderly (above 60 years of age), have received an organ transplant, have kidney problems or if you are being treated with corticosteroids. Inflammation and ruptures of tendons may occur within the first 48 hours of treatment and even up to several months after stopping of [product name] therapy. At the first sign of pain or inflammation of a tendon (for example in your ankle, wrist, elbow, shoulder or knee), stop taking [product name], contact your healthcare providers and rest the painful area. Avoid any unnecessary exercise as this might increase the risk of a tendon rupture.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Peripheral neuropathy You may rarely experience symptoms of nerve damage (neuropathy) such as pain, burning, tingling, numbness and/or weakness especially in the feet and legs or hands and arms. If this happens, stop taking [product name] and inform your healthcare providers immediately in order to prevent the development of potentially irreversible condition. **c) Side Effects:** Fluoroquinolones have been reported to cause serious side effects involving tendons, muscles, joints, and the nerves – in a small proportion of patients, these side effects caused long-lasting or permanent disability (see section Before you start to use it and Things to be careful of). **References:** **Directive No. 10, 2011.** ***Bil. (20) dlm. BPFK/PPP/01/03 Jilid 1*** *Direktif untuk Memperkukuhkan Amaran Berkaitan dengan Exacerbation of Myasthenia Gravis dalam Sisip Bungkusan Semua Produk Antibiotik dalam Kumpulan Fluoroquinolones* **Directive No. 9, 2019.** ***BPFK/PPP/07/25 (9) Jld.3*** *Direktif Untuk Semua Produk Yang Mengandungi Antibiotik Kumpulan Fluoroquinolone (Sediaan Oral Dan Injeksi Sahaja): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Aortic Aneurysm dan Aortic Dissection* **Directive No. 12, 2019.** ***BPFK/PPP/07/25 (12) Jld.3*** *Direktif Untuk Semua Produk Yang Mengandungi Fluoroquinolone (Sediaan Oral Dan Injeksi): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berikut: a) Membatalkan dan Menghadkan Indikasi Antibiotik Kumpulan Fluoroquinolone b) Amaran Berkaitan Disabling and Potentially Permanent Side Effects (Tendinitis, Tendon Rupture, Peripheral Neuropathy & Central Nervous System/ Neuropsychiatric Effects)*
83.	**GABAPENTIN** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing Gabapentin; **Package Insert** **a) Warnings and Precautions:** Respiratory depression Gabapentin has been associated with severe respiratory depression. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of central nervous system (CNS) depressants and the elderly might be at higher risk of experiencing this severe adverse reaction. Dose adjustments might be necessary in these patients.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	b) Adverse Effects/ Undesirable Effects: Respiratory, thoracic and mediastinal disorders Frequency 'rare': Respiratory depression Post-marketing experience: Dysphagia **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [product name]:** Before you start to use it If you have kidney problems, nervous system disorders, respiratory disorders or you are more than 65 years old, your doctor may prescribe a different dosing regimen. Tell your doctor or pharmacist if you are taking or have been recently taking any medicines for convulsions, sleeping disorders, depression, anxiety, or any other neurological or psychiatric problems. **b) Side Effects:** Contact your doctor immediately or go to the Emergency Department of your nearest hospital if you experience breathing problems such as slow, shallow or weak breathing after taking this medicine as this can be a sign of respiratory depression. **References:** **Directive No. 9, 2018**. ***BPFK/PPP/07/25 (9) Jld. 2*** *Direktif Untuk Semua Produk Yang Mengandungi Gabapentin: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Respiratory Depression* **Directive No. 5, 2020**. ***BPFK/PPP/07/25 (5) Jld. 4*** *Direktif Untuk Semua Produk Yang Mengandungi Gabapentin: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Penambahan Maklumat Keselamatan Berkaitan Risiko Dysphagia*
84.	**GADOBENIC ACID** **Indication** of products containing gadobenic acid shall be amended as follows: a) [Product name] is a paramagnetic contrast agent for use in diagnostic magnetic resonance imaging (MRI) of the liver for the detection of focal liver lesions in patients with known or suspected primary liver cancer (e.g. hepatocellular carcinoma) or metastatic disease. [Product name] should be used only when diagnostic information is essential and not available with unenhanced MRI and when delayed phase imaging is required.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	b) Other indications including use in MRI of the brain and spine, as contrast-enhanced MR- angiography & MRI of the breast shall be removed.
85.	**GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING** The following boxed warning and warning shall be included in the package inserts of products containing Gadolinium Based Contrast Medium for Magnetic Resonance Imaging: **BOXED WARNING** - Exposure to gadolinium – based contrast agents (GBCAs) increases the risk for Nephrogenic Systemic Fibrosis (NSF) in patients with: • acute or chronic severe renal insufficiency (glomerular filtration rate < 30mL/min/1.73m^2), or • acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period. - NSF is a debilitating and sometimes fatal disease affecting the skin, muscle, and internal organs - Avoid use of GBCAs unless the diagnotic information is essential and not available with non-contrast enhanced magnetic resonance imaging (MRI). - Screen all patients for renal dysfunction by obtaining a history and/ or laboratory tests. - When administering a GBCA, do not exceed the dose recommended in product labelling. Allow sufficient time for elimination of the GBCA prior to any readministration. **WARNINGS AND PRECAUTIONS** • Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a GBCA. • For patients receiving haemodialysis, healthcare professionals may consider prompt haemodialysis following GBCA administration in order to enhance the contrast agent's elimination. However, it is unknown if haemodialysis prevents NSF.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	• Determine the renal function of patients by obtaining a medical history of conducting laboratory tests that measure renal function prior to using GBCA. • The risk, if any, for developing NSF among patients with mild to moderate renal insufficiency or normal renal function is unknown. • Post-marketing reports have identified the development of NSF following single and multiple administrations of GBCAs. **Reference:** ***Bil. (2) dlm. BPFK/PPP/01/03 Jld. 1*** *Keputusan Mesyuarat PBKD - Penambahan Amaran Berkotak dan Amaran Terkini Ke Dalam Sisip Bungkusan Semua Agen 'Contrast Medium' Yang Berasaskan 'Gadolinium' (Gadolinium Based) Untuk Tujuan 'Magnetic Resonance Imaging'*
86.	**GAMAT/ STICHOPUS spp.** For products containing Gamat/ Stichopus spp. for **ORAL USE ONLY**, please state: **"Please consult your pharmacist, doctor, or other healthcare providers about any other supplements/ medications you are taking and other health care problems. There may be a potential for interactions or side effects."**
87.	**GENTAMICIN TOPICAL PREPARATIONS** The following boxed statement shall be included in the package inserts of topical Gentamicin preparations: Use of topical gentamicin preparations in closed hospital settings is actively discouraged
88.	**GINKGO BILOBA/ GINKGO EXTRACT** The following statements shall be included on the labels and in the package inserts of products containing *Gingko biloba*/ Gingko extract: As the use of Ginkgo may increase the tendency of bleeding, please consult your physician/ pharmacist if you are on or intend to start using any other medicines and before you undergo any surgical/dental procedure. (*Memandangkan Ginkgo boleh meningkatkan kemungkinan pendarahan, sila rujuk kepada doktor/ ahli farmasi sekiranya anda sedang atau akan menggunakan ubat lain dan sebelum prosedur pembedahan / dental dijalankan*). **Reference:** ***Bil. (47) dlm. BPFK/02/5/1.3*** *Pernyataan Amaran Pada Label dan Sisip Bungkusan Produk Yang Mengandungi Ginkgo Biloba / Ginkgo Ekstrak*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
89.	**GINSENG** The following statements shall be included on the labels and in the package inserts of products containing Ginseng (including all Panax genus): • Contraindicated in pregnant women. • Safe use in lactating women and children has not been established. • Do not exceed the stated dose. • Safety on long term use has not been established.
90.	**GLUCOSAMINE** The following statement shall be included on the labels and package inserts of products containing Glucosamine (derived from seafood); **"DERIVED FROM SEAFOOD"** The following statement shall be included in the package inserts of products containing Glucosamine: **ADVERSE EFFECTS/ UNDESIRABLE EFFECTS:** • Cardiovascular Peripheral oedema, tachycardia were reported in a few patients following larger clinical trials investigating oral administration in osteoarthritis. Causal relationship has not been established. • Central nervous system Drowsiness, headache, insomnia have been observed rarely during therapy (less than 1%). • Gastrointestinal Nausea, vomiting, diarrhoea, dyspepsia or epigastric pain, constipation, heartburn and anorexia have been described rarely during oral therapy with glucosamine. • Skin Skin reactions such as erythema and pruritus have been reported with therapeutic administration of glucosamine. **References:** ***Bil. (52) dlm. BPFK/02/5/1.3*** *Muatkan Kenyataan 'Derived From Seafood' Pada Label Produk Jika Bahan AKtif Adalah Daripada Sumber Laut* ***Bil. (72) dlm. BPFK/02/5/1.3*** *Keputusan Mesyuarat PBKD - Mengemaskini dan Menyelaraskan Maklumat Mengenai Kesan Sampingan Pada Label dan Sisip Bungkusan Produk Yang Mengandungi Glucosamine*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
91.	**HIV PROTEASE INHIBITORS** The following statement shall be included in the package inserts of products containing HIV Protease inhibitors: **ADVERSE EFFECTS/ UNDESIRABLE EFFECTS:** Although a causal relationship has not been definitively established, protease inhibitors may contribute to increase in blood sugar levels and even diabetes in HIV patients. Close monitoring of blood glucose level is recommended.
92.	**HYDROCHLOROTHIAZIDE** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing hydrochlorothiazide; **Package Insert** **a) Warnings and Precautions:** Non-melanoma skin cancer An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC. Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC. **b) Adverse Effects/ Undesirable Effects:** Neoplasms benign, malignant and unspecified (incl cysts and polyps) Frequency 'not known': Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Description of selected adverse reactions Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. **c) Pharmacodynamic:** Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg). **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Before you use [product name]:** Inform your healthcare providers before taking [product name] if you have had skin cancer or if you develop an unexpected skin lesion during the treatment. Treatment with hydrochlorothiazide, particularly long term use with high doses, may increase the risk of some types of skin and lip cancer (non-melanoma skin cancer). Protect your skin from sun exposure and UV rays while taking [product name]. **b) Side Effects:** Frequency 'not known': Skin and lip cancer (Non-melanoma skin cancer) **Reference: Directive No. 11, 2019.** ***BPFK/PPP/07/25 (11) Jld.3*** *Direktif Untuk Semua Produk Yang Mengandungi Hydrochlorothiazide Termasuk Kombinasi: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Penambahan Maklumat Keselamatan Berkaitan Non-Melanoma Skin Cancer*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
93.	**HYDROQUINONE** The following warning shall be included on the outer labels of products containing Hydroquinone: **WARNING:** Some users of this product may experience skin irritations. Should this occur, stop using and consult a medical doctor. For hydroquinone products that do not contain any sun screening agent, a statement should be included in the package insert to advise users to either use a sun screening agent or protect themselves from sunlight or to use the products only at night. **Reference:** ***Bil. (26) dlm.BPFK/02/5/1.2*** *Amaran bagi Produk Mengandungi Hydroquinone*
94.	**HYOSCINE (FOR INJECTION ONLY)** The following statements shall be included in the package insert of products containing Hyoscine: **Package Insert** **a) Contraindications:** [Product name] should not be administered to patients with tachycardia. **b) Warnings and Precautions:** [Product name] can cause tachycardia, hypotension and anaphylaxis, therefore use with caution in patients with cardiac conditions such as cardiac failure, coronary heart disease or cardiac arrhythmia and patients with cardiovascular disease (e.g. acute myocardial infarction, hypertension and conditions associated with tachycardia or hypertension, and in cardiac surgery). Monitoring of these patients is advised. Emergency equipment and personnel trained in its use must be readily available. **c) Adverse Effects/Undesirable Effects:** Immune system disorders Not known: anaphylactic shock including cases with fatal outcome, anaphylactic reactions. Cardiac disorders Common: tachycardia **Reference: Directive No. 17, 2017.** ***BPFK/PPP/07/25 (22) Jld. 1*** *Direktif Untuk Semua Produk Yang Mengandungi Hyoscine (Bentuk Dos Injeksi Sahaja): Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Risiko Kesan Advers Serius Pada Pesakit Jantung dan Kardiovaskular*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
95.	**IMMUNOSUPPRESANTS** The following information shall be included in the package inserts of products containing immunosuppressants: **WARNINGS AND PRECAUTIONS** Immunosuppressed patients are at increased risk for opportunistic infections, including activation of latent viral infections. These include BK virus associated nephropathy which has been observed in patients receiving immunosuppressants. These infections may lead to serious, including fatal outcomes. **Reference:** ***Bil. (44) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Berkaitan Dengan "Increased Risk for Opportunistic Infections Such As Activation of Latent Viral Infections Including BK Virus – Associated Nephropathy" Yang Perlu Dimuatkan Pada Sisip Bungkusan Produk Immunosuppressant*
96.	**INSULIN (INCLUDING COMBINATION PRODUCTS)** The label of the product shall state clearly the source of insulin. The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing insulin (including combination products); **Package Insert** **a) Posology and Method of Administration:** Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis. **b) Warnings and Precautions:** Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site, and dose adjustment of antidiabetic medications may be considered. **c) Adverse Effects/ Undesirable Effects:**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Skin and subcutaneous tissue disorders Frequency "not known": Cutaneous amyloidosis Description of selected adverse reactions Lipodystrophy and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions. **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [product name]:** Before you start to use it Skin changes at the injection site: The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area. Contact your doctor if you are currently injecting into a lumpy area before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose. **b) Side effects:** Frequency 'not known': Changes at the injection site (Cutaneous amyloidosis) **Reference: Directive No. 18, 2021**. ***NPRA.600-1/9/13(28)*** *Direktif Untuk Semua Produk Yang Mengandungi Insulin (Termasuk Produk Kombinasi): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Cutaneous Amyloidosis*
97.	**INGREDIENTS DERIVED FROM SEAFOOD** The following statement shall be included on the labels and package inserts of products containing ingredients derived from seafood. **"DERIVED FROM SEAFOOD"** **Reference:** ***Bil. (52) dlm. BPFK/02/5/1.3*** *Muatkan Kenyataan 'Derived From Seafood' Pada Label Produk Jika Bahan Aktif Adalah Daripada Sumber Laut*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
98.	**INTERFERON ALPHA** The following statements shall be included in the package insert and RiMUP of products containing Interferon Alpha: **Package Insert** **a) Adverse Effects/ Undesirable Effects:** **Respiratory, thoracic and mediastinal disorders:** Frequency 'not known': Pulmonary arterial hypertension (class label for interferon products). Cases of pulmonary arterial hypertension (PAH) have been reported with interferon alpha products, notably in patients with risk factors for PAH (such as portal hypertension, HIV infection, cirrhosis). Events were reported at various time points typically several months after starting treatment with interferon alpha. **Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects** Tell your doctor immediately if you experience: • Shortness of breath, persistent coughing, fatigue, chest pain, or swelling of the ankles, limbs and abdomen. These may indicate pulmonary arterial hypertension (high blood pressure in the arteries that supply the lungs). **Reference: Directive No. 1, 2017.** ***BPFK/PPP/07/25 (6) Jld. 1*** *Direktif Bagi Semua Produk Yang Mengandungi Interferon Alfa dan Interferon Beta: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna Dengan Maklumat Keselamatan Berkaitan Risiko Kesan Advers Pulmonary Arterial Hypertension (PAH)*
99.	**INTERFERON BETA** The following statements shall be included in the package insert and RiMUP of products containing Interferon Beta: **Package Insert** **a) Adverse Effects/ Undesirable Effects:** **Respiratory, thoracic and mediastinal disorders:** Frequency 'not known': Pulmonary arterial hypertension (class label for interferon products). Cases of pulmonary arterial hypertension (PAH) have been reported with interferon beta products. Events were reported at various time points including up to several years after starting treatment with interferon beta.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Consumer Medication Information Leaflet (RiMUP) **a) Side Effects** Tell your doctor immediately if you experience: • Shortness of breath, persistent coughing, fatigue, chest pain, or swelling of the ankles, limbs and abdomen. These may indicate pulmonary arterial hypertension (high blood pressure in the arteries that supply the lungs). **Reference: Directive No. 1, 2017.** ***BPFK/PPP/07/25 (6) Jld. 1*** *Direktif Bagi Semua Produk Yang Mengandungi Interferon Alfa dan Interferon Beta: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna Dengan Maklumat Keselamatan Berkaitan Risiko Kesan Advers Pulmonary Arterial Hypertension (PAH)*
100.	**IODINATED CONTRAST MEDIA** The following statements shall be included in the package insert for products containing Iodinated Contrast Media; **Package Insert** **a) Adverse Effects/Undesirable Effects:** Skin and Subcutaneous Tissue Disorders Severe cutaneous adverse reactions {e.g. Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP)} have been reported in post-marketing experience of iodinated contrast media. **Reference: Directive No. 24, 2018.** ***Bil. (24) dlm. BPFK/PPP/07/25 (24) Jld.2*** *Direktif Untuk Semua Produk Yang Mengandungi Iodinated Contrast Media: Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Severe Cutaneous Adverse Reactions (SCARs)*
101.	**ISONIAZID** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing Isoniazid: **Package Insert** **a) Adverse Effects/Undesirable Effects:** Gastrointestinal Disorders: Pancreatitis

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Consumer Medication Information Leaflet (RiMUP) **a) Side Effects:** Inflammation of the pancreas, which causes severe pain in the abdomen and back (pancreatitis) **Reference : Directive No. 27, 2018.** ***BPFK/PPP/07/25 (27) Jld.2*** *Direktif Untuk Semua Produk Yang Mengandungi Isoniazid: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RIMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Pancreatitis*
102.	**KAOLIN, PECTIN, KAOLIN-PECTIN** The following boxed warning shall be included on the labels: **NOT RECOMMENDED FOR CHILDREN UNDER 6 YEARS OF AGE.** The following statement shall be included in the package inserts of products containing kaolin and/ or pectin: **WARNING** **Not recommended for children under 6 years of age.** Severe constipation, which may lead to faecal impaction, may rarely occur in children and the elderly patients taking kaolin and pectin. Kaolin and pectin may interfere with the absorption of other drugs, including antibiotics, administered concurrently. **PRECAUTION** Appropriate fluid and electrolyte therapy should be given to protect against dehydration. Oral rehydration therapy with the use of appropriate fluids including oral rehydration salts - remains the most effective treatment for dehydration due to diarrhoea. The intake of as much of these fluids as possible is therefore imperative.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
103.	**KETOCONAZOLE** **1) Indication of products containing oral ketoconazole is restricted as follows, and the package insert of the product shall be amended accordingly:** [BRAND NAME] (ketoconazole) Tablets should be used only when other effective antifungal therapy is not available or tolerated and the potential benefits are considered to outweigh the potential risks. [BRAND NAME] (ketoconazole) Tablets are indicated for the treatment of the following systemic fungal infections in patients who have failed or who are intolerant to other therapies: blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis. [BRAND NAME] (ketoconazole) Tablets should not be used for fungal meningitis because it penetrates poorly into the cerebrospinal fluid. **Reference: Directive No. 3, 2014.** ***Bil. (9)dlm.BPFK/PPP/07/25*** *Direktif Untuk Memperketatkan Indikasi Semua Produk Ketoconazole Oral Dan Mengehadkan Penggunaan Di Hospital Sahaja Berikutan Risiko Kesan Advers Hepatotoksisiti* **2) The following statement shall be included in the package inserts of products containing oral ketoconazole:** **CONTRAINDICATIONS** In patients with acute or chronic liver disease. **WARNINGS AND PRECAUTIONS** Because of the risk for serious hepatotoxicity, [BRAND NAME] should be used only when the potential benefits are considered to outweigh the potential risks, taking into consideration the availability of other effective antifungal therapy. Assess liver function, prior to treatment to rule out acute or chronic liver disease, and monitor at frequent and regular intervals during treatment, and at the first signs or symptoms of possible hepatotoxicity. **Hepatotoxicity** Very rare cases of serious hepatotoxicity, including cases with a fatal outcome or requiring liver transplantation have occurred with the use of oral ketoconazole. Some patients had no obvious risk factors for liver disease. Cases have been reported that occurred within the first month of treatment, including some within the first week.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	The cumulative dose of the treatment is a risk factor for serious hepatotoxicity. Factors which may increase the risk of hepatitis are prolonged treatment with ketoconazole tablets, females over 50 years of age, previous treatment with griseofulvin, a history of liver disease, known drug intolerance and concurrent use of medication which compromises liver function. A period of one month should be allowed between cessation of griseofulvin treatment and commencement treatment with ketoconazole tablets because of an apparent association between recent griseofulvin therapy and hepatic reactions to ketoconazole tablets. Monitor liver function in all patients receiving treatment with ketoconazole tablets (see Monitoring of hepatic function). Patients should be instructed to promptly report to their physician signs and symptoms suggestive of hepatitis such as anorexia, nausea, vomiting, fatigue, jaundice, abdominal pain or dark urine. In these patients, treatment should be stopped immediately and liver function should be conducted. **Monitoring of hepatic function** Monitor liver function in all patients receiving treatment with ketoconazole tablets. Monitor liver function prior to treatment to rule out acute or chronic liver disease (see CONTRAINDICATIONS), after two weeks of treatment and then on a monthly basis and at the first signs or symptoms of possible hepatic toxicity. When the liver function tests indicate liver injury, the treatment should be stopped immediately. A risk and benefit evaluation should be made before oral ketoconazole is used in cases of non-life threatening diseases requiring long treatment periods. In patients with elevated liver enzymes, or who have experienced liver toxicity with other drugs, treatment should not be started unless the expected benefit exceeds the risk of hepatic injury. In such cases, close monitoring of the liver enzymes is necessary. **ADVERSE EFFECTS/ UNDESIRABLE EFFECTS** **Post-marketing Experience** ***Hepato-biliary Disorders*** Very rare: serious hepatotoxicity, including hepatitis cholestatic, biopsy-confirmed hepatic necrosis, cirrhosis, hepatic failure including cases resulting in transplantation or death (see WARNINGS AND PRECAUTIONS). **Reference: Directive No. 12, 2011.** ***Bil. (22)dlm.BPFK/PPP/01/03 Jilid 1*** *Direktif Memperkukuhkan Amaran Berkaitan Dengan Risiko Hepatotoksisiti Yang Teruk Dalam Sisip Bungkusan Semua Produk Oral Ketoconazole*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
104.	**KETOROLAC TROMETHAMOL (KETOROLAC TROMETHAMINE)** The following statements shall be included in the package inserts of products containing Ketorolac tromethamol: **THE PRODUCT SHALL BE INDICATED FOR THE FOLLOWING** For short-term management of moderate to severe acute post-operative pain following surgical procedures associated with low risk of haemorrhage. **DOSAGE AND DURATION OF TREATMENT** Parenteral administration: The starting dose should be 10mg with subsequent doses of 10-30mg four to six hourly as required. The lowest effective dose should be used. The total daily dose of 90mg for the non-elderly and 60mg for the elderly should not be exceeded. Maximum duration of parenteral treatment is 2 days for all age groups. In patients who have received parenteral ketorolac and are converted to oral tablets, the total combined daily dose of all forms of ketorolac should not exceed 90mg for non-elderly and 60mg for the elderly. Maximum duration of treatment for the oral formulation is 7 days. **CONTRAINDICATIONS** • A history of peptic ulceration or gastrointestinal bleeding • A history of haemorrhagic diathesis • A history of confirmed or suspected cerebrovascular bleeding • Operations associated with a high risk of haemorrhage • A history of asthma • Moderate or severe renal impairment (serum creatinine > 160 mol/L) • Hypovolaemia or dehydration from any cause • Hypersensitivity to NSAIDs or aspirin • During pregnancy, labour, delivery or lactation • Concomitant administration with other NSAIDs, anticoagulant including low dose heparin

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
105.	**LAMOTRIGINE** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing lamotrigine; **Package Insert** **a) Warnings and Precautions:** Hemophagocytic lymphohistiocytosis (HLH) has occurred in patients taking lamotrigine (see section Adverse Effects/Undesirable Effects). HLH is a syndrome of pathological immune activation, which can be life threatening, characterised by clinical signs and symptoms such as fever, rash, neurological symptoms, hepatosplenomegaly, lympha-denopathy, cytopenias, high serum ferritin, hypertriglyceridaemia and abnormalities of liver function and coagulation. Symptoms occur generally within 4 weeks of treatment initiation. Immediately evaluate patients who develop these signs and symptoms and consider a diagnosis of HLH. Lamotrigine should be discontinued unless an alternative aetiology can be established. **Brugada-type ECG** A very rare association with Brugada-type ECG has been observed, although a causal relationship has not been established. Therefore, careful consideration should be given before using [product name] in patients with Brugada syndrome. **b) Adverse Effects/Undesirable Effects:** **Post-marketing** Blood and lymphatic system disorders Very rare: Hemophagocytic lymphohistiocytosis (see section Warnings and Precautions) **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [product name]:** Before you start to use it Talk to your healthcare providers before taking [product name]: • If you have a condition called Brugada syndrome (a genetic disease that affects the heart)

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	b) Side Effects: Hemophagocytic lymphohistiocytosis (HLH) There have been reports of a rare but very serious immune system reaction, in patients taking lamotrigine. - Contact your doctor or pharmacist immediately if you experience any of the following symptoms while taking lamotrigine: fever, rash, neurological symptoms (e.g. shaking or tremor, confusional state). **References:** **Directive No. 3, 2019.** ***BPFK/PPP/07/25 (3) Jld.3*** *Direktif Untuk Semua Produk Yang Mengandungi Lamotrigine: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Hemophagocytic Lymphohistiocytosis (HLH)* **Directive No. 14, 2019.** ***BPFK/PPP/07/25 (14) Jld.3*** *Direktif Untuk Semua Produk Yang Mengandungi Lamotrigine: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Penambahan Maklumat Keselamatan Berkaitan Risiko Brugada-Type ECG*
106.	**LENOGRASTIM** The following statements shall be included in the package insert of products containing Lenograstim; **a) Warnings and Precautions:** Aortitis has been reported after G-CSF administration in healthy subjects and in cancer patients. The symptoms experienced included fever, abdominal pain, malaise, back pain and increased inflammatory markers (e.g. C-reactive protein and white blood cell count). In most cases aortitis was diagnosed by CT scan and generally resolved after withdrawal of G-CSF. **b) Adverse Effects/Undesirable Effects:** Vascular disorders Frequency "rare": Aortitis **Reference: Directive No. 30, 2018.** ***Bil. (30) dlm. BPFK/PPP/07/25 Jld.2*** *Direktif Untuk Semua Produk Yang Mengandungi Filgrastim, Pegfilgrastim dan Lenograstim: Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Aortitis*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
107.	**LEVETIRACETAM** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing Levetiracetam; **Package Insert** **a) Warnings and Precautions:** Acute kidney injury The use of levetiracetam has been rarely associated with acute kidney injury, with a time to onset ranging from a few days to several months. **b) Adverse Effects / Undesirable Effects:** Renal and urinary disorders: Frequency rare: acute kidney injury. Musculoskeletal and connective tissue disorders: Frequency rare: rhabdomyolysis and blood creatine phosphokinase increased.* * Prevalence is significantly higher in Japanese patients when compared to non-Japanese patients. Cases of encephalopathy have been rarely observed after levetiracetam administration. These undesirable effects generally occurred at the beginning of the treatment (few days to a few months) and were reversible after treatment discontinuation. **Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects:** Tell your doctor immediately if you notice any of the following: • Symptoms such as low urine volume, tiredness, nausea, vomiting, confusion and swelling in the legs, ankles or feet, may be a sign of sudden decrease of kidney function. • Signs or symptoms including muscleache, feeling of weakness and dark urine may indicate the side effect of rhabdomyolysis (breakdown of muscle tissue). • If someone around you notices signs of confusion, somnolence (sleepiness), amnesia (loss of memory), memory impairment (forgetfulness), abnormal behaviour or other neurological signs including involuntary or uncontrolled movements, these could be symptoms of an encephalopathy. **Reference: Directive No. 3, 2018.** ***BPFK/PPP/07/25 (3) Jld.2*** *Direktif Untuk Semua Produk Yang Mengandungi Levetiracetam: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Acute Kidney Injury, Rhabdomyolysis/ Blood Creatine Phosphokinase Increased dan Encephalopathy*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
108.	**LEVONORGESTREL** The following statements shall be included in the package insert, label and RiMUP of emergency contraceptives containing Levonorgesteral: **Package Insert** **a) Recommended Dose:** Women who have used enzyme-inducing drugs during the last 4 weeks and need emergency contraception are recommended to use a non-hormonal emergency contraceptive, i.e. Cu-IUD or take a double dose of levonorgestrel (i.e. <number of> tablets taken together) for those women unable or unwilling to use Cu-IUD. **b) Interactions:** The metabolism of levonorgestrel is enhanced by concomitant use of liver enzyme inducers, mainly CYP3A4 enzyme inducers. Concomitant administration of efavirenz has been found to reduce plasma levels of levonorgestrel (AUC) by around 50%. Drugs suspected of having similar capacity to reduce plasma levels of levonorgestrel include barbiturates, phenytoin, carbamazepine, herbal medicines containing Hypericum perforatum (St. John's wort), rifampicin, ritonavir, and griseofulvin. For women who have used enzyme-inducing drugs in the past 4 weeks and need emergency contraception, the use of non-hormonal emergency contraception (i.e. a Cu-IUD) should be considered. Taking a double dose of levonorgestrel (i.e. 3 mg within 72 hours after the unprotected intercourse) is an option for women who are unable or unwilling to use a Cu-IUD, although this specific combination (a double dose of levonorgestrel during concomitant use of an enzyme inducer) has not been studied. **Label** *If you have used certain **other medicines in the last 4 weeks**, in particular treatment for epilepsy, tuberculosis, for HIV infection or herbal medicines containing St. John´s wort (see leaflet), [product name] may work less effectively. If you use these medicines take <number of> tablets of [product name]. If you are unsure or to ask for an alternative treatment speak to your doctor or pharmacist before using [product name].*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Consumer Medication Information Leaflet (RiMUP) **a) Before you use [product name]** **Taking other medicines** If you have used any of the medicines below during the last 4 weeks, [product name] may work less effectively.Your doctor may prescribe another type of (non-hormonal) emergency contraceptive, i.e. a copper intrauterine device (Cu-IUD). If this is not an option for you or if you are unable to see your doctor promptly, you can take a double dose (i.e. <number of> tablets) of [product name]: • medicines used to treat epilepsy (e.g. phenobarbitone, phenytoin, carbamazepine) • medicines used to treat tuberculosis (e.g. rifampicin) • medicines used to treat HIV (e.g. ritonavir, efavirenz) • medicines used to treat fungal infections (e.g. griseofulvin) • herbal remedies containing St. John's wort (Hypericum perforatum) Speak to your doctor or pharmacist if you need further advice on the correct dose for you. Consult your doctor as soon as possible after taking the tablets for further advice on a reliable form of regular contraception and to exclude a pregnancy. **Reference: Directive No. 11, 2017.** ***BPFK/PPP/07/25 (16) Jld.1*** *Direktif Untuk Semua Produk Kontraseptif Kecemasan Yang Mengandungi Levonorgestrel Dengan Maklumat Berkaitan Interaksi Antara Ubat-Ubatan Yang Dikelaskan Sebagai Hepatic Enzyme Inducer Dan Keberkesanan Kontrasepsi*
109.	**LINCOMYCIN** For all products containing Lincomycin: The package insert must emphasize the possibility of pseudomembranous colitis with the use of the drug and must include the following boxed or emphasized statement/ warning: a. Lincomycin therapy has been associated with severe colitis which may end fatally. b. It should be reserved for serious infections where less toxic antimicrobial agents are inappropriate. c. It should not be used in patients with nonbacterial infections, such as most upper respiratory tract infections. d. Its use in newborns is contraindicated.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
110.	**LIQUID PARAFFIN** The following statement shall be included on the labels of products containing Liquid paraffin as laxative: • Not recommended for use in children below 3 years of age; • Not recommended for use in pregnant women; • Repeated use is not advisable; • Consult your doctor if laxatives are needed every day, if you have persistent abdominal pain or have a condition which makes swallowing difficult.
111.	**LOPERAMIDE** 1. The following boxed warning shall be included on the labels of products containing Loperamide: **NOT RECOMMENDED FOR CHILDREN UNDER 6 YEARS OF AGE** 2. The following statement shall be included in the package inserts of products containing Loperamide: **a) WARNING** Not recommended for children under 6 years of age. Its use has been associated with fatal episodes of paralytic ileus in infants and young children. **b) PRECAUTION** Appropriate fluid and electrolyte therapy should be given to protect against dehydration in all cases of diarrhoea. Oral rehydration therapy which is the use of appropriate fluids including oral rehydration salts remains the most effective treatment for dehydration due to diarrhoea. The intake of as much of these fluids as possible is therefore imperative. Drug-induced inhibition of peristalsis may result in fluid retention in the intestine, which may aggravate and mask dehydration and depletion of electrolytes. If severe dehydration or electrolyte imbalance is present Loperamide should be withheld until appropriate corrective therapy has been initiated. **c) Warnings and Precautions** The use of higher than the recommended doses for control of the diarrhea may cause abnormal heart rhythms and serious cardiac events leading to

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	death. However, in adult patients receiving the recommended dosage of loperamide, cases of syncope and ventricular tachycardia have been reported. Some of these patients were taking other drugs or had other risk factors that may have increased their risk of cardiac adverse reactions. Abuse and misuse of loperamide, as an opioid substitute, have been described in individuals with opioid addiction (see Overdose). **d) Adverse Effects/ Undesirable Effects** Post-marketing Experience Cardiac Disorders: QT/QTc interval prolongation, Torsades de Pointes, other ventricular arrhythmias, cardiac arrest, syncope, and death (see Warnings and Precautions) **e) Overdose** In individuals who have intentionally ingested overdoses (reported in doses from 40 mg up to 792 mg per day) of loperamide HCL, prolongation of the QT/QTc interval, Torsades de Pointed, other ventricular arrhythmias and cardiac arrest, have been observed (see Warnings and Precautions). Fatal cases have also been reported. Abuse, misuse and/or overdose with excessively large doses of loperamide, may unmask Brugada syndrome. 3. The following statement shall be included in the RiMUP of products containing Loperamide: **a) If you use too much (overdose)** If you have taken more than the recommended dose of [product name], immediately contact your doctor or go to the Emergency Department of your nearest hospital for advice. Symptoms may include : • changes to your heartbeat such as increased heart rate and irregular heart rhythm (these symptoms can have potentially serious, life-threatening consequences) • muscle stiffness • uncoordinated movements • drowsiness • difficulty urinating • weak breathing

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	References: **Directive No. 14, 2017.** ***BPFK/PPP/07/25 (19) Jld.1*** *Direktif Untuk Semua Produk Farmaseutikal Yang Mengandungi Loperamide: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Risiko Kesan Advers Pada Jantung Yang Serius Susulan Pengambilan Loperamide Melebihi Dos Yang Disyorkan dan Isu Penyalahgunaan* **Directive No. 18, 2019.** ***BPFK/PPP/07/25 (18) Jld.3*** *Direktif Untuk Semua Produk Yang Mengandungi Loperamide: Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Unmasking Brugada Syndrome Dengan Pengambilan Dos Berlebihan*
112.	**LOVASTATIN** The following statement shall be included in the package inserts of products containing Lovastatin: **1. Contraindications:** • Concomitant administration of strong CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone). • Concomitant administration of cyclosporine. **2. Dosage and Administration:** Concomitant Therapy The combined use of lovastatin with gemfibrozil should be avoided. In patients taking danazol, verapamil, diltiazem, fibrates (except gemfibrozil) or lipid-lowering dose of niacin (≥1g/day) concomitantly with [Product Name], the dose of [Product Name] should not exceed 20mg/day. In patients taking amiodarone concomitantly with [Product Name], the dose of [Product Name] should not exceed 40mg/day. **3. Warnings and Precautions:** Colchicine: Cases of myopathy, including rhabdomyolysis, have been reported with lovastatin coadministered with colchicine, and caution should be exercised when prescribing lovastatin with colchicine. **4. Interactions:** Contraindicated Drugs Strong inhibitors of CYP3A4: Concomitant use with strong CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone) is contraindicated.

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	Cyclosporine: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of cyclosporine. Concomitant use of this drug with lovastatin is contraindicated. Other Drugs • Gemfibrozil, other fibrates, niacin ≥1g/day: These drugs increase the risk of myopathy when given concomitantly with lovastatin, probably because they can produce myopathy when given alone. There is no evidence to suggest that these agents affect the pharmacokinetics of lovastatin. Myopathy, including rhabdomyolysis, has occurred in patients who were receiving coadministration of lovastatin with fibric acid derivatives or niacin. • Danazol, verapamil, diltiazem: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of danazol, verapamil, or diltiazem particularly with higher doses of lovastatin. • Amiodarone: The risk of myopathy/rhabdomyolysis is increased when amiodarone is used concomitantly with higher doses of a closely related member of the HMG-CoA reductase inhibitor class. • Colchicine: Cases of myopathy, including rhabdomyolysis, have been reported with lovastatin coadministered with colchicine, and caution should be exercised when prescribing lovastatin with colchicine.
113.	**MEFLOQUINE** The following statement shall be included in the package inserts of products containing Mefloquine as single ingredient or in combination with other active ingredients: **1. WARNINGS AND PRECAUTIONS** a) Products containing Mefloquine as single ingredient**:** In chemoprophylaxis the safety profile of mefloquine is characterized by a predominance of neuropsychiatric adverse reactions. If acute anxiety, depression, restlessness or confusion occur during prophylactic use, **[Brand name] (mefloquine)** should be discontinued and an alternative prophylactic agent should be recommended. Because of the long half-life of mefloquine, adverse reactions to **[Brand name] (mefloquine)** may occur or persist up to several weeks after discontinuation of the drug. In a small number of patients it has been reported that dizziness or vertigo and loss of balance may continue for months after discontinuation of the drug.

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Eye disorders, including but not limited to optic neuropathy and retinal disorders, have been reported during treatment with mefloquine. Any patient presenting with a visual disorder should be referred to the treating physician, as certain conditions may require stopping treatment with **[Brand name] (mefloquine)**.

b) Products containing Mefloquine in combination with other active ingredientas (mefloquine/artesunate):

If acute anxiety, depression, restlessness or confusion occur during treatment, **[Brand name] (mefloquine/artesunate)** should be discontinued and an alternative agent should be recommended. Because of the long half-life of mefloquine, adverse reactions to **[Brand name] (mefloquine/artesunate)** may occur or persist up to several weeks after discontinuation of the drug. In a small number of patients it has been reported that dizziness or vertigo and loss of balance may continue for months after discontinuation of the drug.

Eye disorders, including but not limited to optic neuropathy and retinal disorders, have been reported during treatment with mefloquine. Any patient presenting with a visual disorder should be referred to the treating physician, as certain conditions may require stopping treatment with **[Brand name] (mefloquine/artesunate).**

2. POSTMARKETING ADVERSE EVENT

Nervous system disorders	
Common	Dizziness, headache
Not known	Balance disorder, somnolence, syncope, convulsions, memory impairment, peripheral sensory neuropathy and peripheral motor neuropathy (including paraesthesia, tremor and ataxia), encephalopathy
Eye disorders	
Common	Visual impairment
Not known	Vision blurred, cataract, retinal disorders and optic neuropathy which may occur with latency during or after treatment

Reference: ***Bil. (13) dlm.BPFK/PPP/01/03 Jld.3*** *Pengemaskinian Sisip Bungkusan Semua Produk Antimalaria Yang Mengandungi Mefloquine (Termasuk Produk Kombinasi) Dengan Maklumat Keselamatan Berkaitan Kesan Advers Pada Sistem Saraf (Neurologik) Yang Berpanjangan dan Gangguan Penglihatan*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
114.	**MELALEUCA LEUCADENDRA** The following statement shall be included on the labels of products containing Melaleuca Leucadendra (cajeput oil) in topical dosage form: a) Malay language: **AMARAN** **Produk ini tidak boleh disapu pada muka, khususnya di kawasan hidung bayi dan kanak-kanak. Ia mungkin boleh menyebabkan masalah pernafasan/ kesukaran bernafas.** b) English language: **WARNING** **This product should not be applied to the facial area, in particular around the nose of infants and small children. It might cause breathing problem / shortness of breath.** **Reference: Directive No. 13, 2016.** ***Bil. (44) dlm.BPFK/PPP/07/25*** *Direktif Bagi Semua Produk Yang Mengandungi Bahan Aktif Minyak Cajeput (Melaleuca Leucadendra) Dalam Bentuk Dos Topikal Dengan Menambah Kenyataan Amaran Berkaitan Risiko Masalah Pernafasan/ Kesukaran Bernafas*
115.	**MESALAZINE** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing mesalazine; **Package Insert** **a) Warnings and Precautions:** • Photosensitivity More severe reactions are reported in patients with pre-existing skin conditions such as atopic dermatitis and atopic eczema. • Cases of nephrolithiasis have been reported with the use of mesalazine, including stones with a 100% mesalazine content. It is recommended to ensure adequate fluid intake during treatment. **b) Adverse Effects/ Undesirable Effects:** Skin and Subcutaneous Tissue Disorders Frequency "rare": Photosensitivity

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Renal and urinary disorders Frequency 'not known' : Nephrolithiasis **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [product name]:** Before you start to use it - Kidney stones may develop with the use of [product name]. Symptoms may include pain in the sides of the abdomen and blood in the urine. Take care to drink a sufficient amount of liquid during treatment with [product name]. **b) Side Effects:** • Photosensitivity: Itchy eruption and exaggerated sunburn on patches of sun-exposed skin • Kidney stones and associated pain **References:** **Directive No. 12, 2018.** ***BPFK/PPP/07/25 (12) Jld.2*** *Direktif Untuk Semua Produk Yang Mengandungi Mesalazine: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Amaran Kesan Advers Photosensitivity* **Directive No. 1, 2021.** ***NPRA.600-1/9/13 (11)*** *Direktif Untuk Semua Produk Yang Mengandungi Mesalazine dan Sulfasalazine: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Nephrolithiasis*
116.	**METFORMIN** The following statements shall be included in the package insert and RiMUP of pharmaceutical products containing Metformin: **Package Insert** **1. Recommended Dosage:** a) Products containing Metformin as a single active ingredient: **Renal impairment** A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

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GFR mL/min	Total maximum daily dose (to be divided into 2-3 daily doses)*	Additional considerations
60-89	3000 mg	Dose reduction may be considered in relation to declining renal function.
45-59	2000 mg	Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of metformin. The starting dose is at most half of the maximum dose.
30-44	1000 mg	
<30	-	Metformin is contraindicated.

* The text "to be divided into 2-3 daily doses" should be omitted for extended release products containing metformin as single agent.

b) Combination products containing Metformin:

Renal impairment

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of metformin in patients with GFR <60 ml/min.

If no adequate strength of [Product name] is available, individual monocomponents should be used instead of the fixed dose combination.

GFR mL/min	Metformin	[other monocomponent]
60-89	Maximum daily dose is 3000 mg. Dose reduction may be considered in relation to declining renal function.	
45-59	Maximum daily dose is 2000 mg. The starting dose is at most half of the maximum dose.	
30-44	Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum dose.	
<30	Metformin is contraindicated.	

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	2. Contraindications: • Severely reduced kidney function (GFR <30 mL/min) • Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis) **3. Warnings and Precautions:** **Lactic acidosis** Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis. In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended. Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis. Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (>5 mmol/L) and an increased anion gap and lactate/pyruvate ratio. **Renal function** GFR should be assessed before treatment initiation and regularly there after [See Section Recommended Dosage]. Metformin is contraindicated in patients with GFR <30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function [See Section Contraindications].

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Consumer Medication Information Leaflet (RiMUP) **a) Before you use [product name]:** When you must not use it: • If you have severely reduced kidney function. • If you have lactic acidosis [too much lactic acid in the blood (see "Risk of lactic acidosis" below)] or ketoacidosis. Ketoacidosis is a condition in which substances called 'ketone bodies' accumulate in the blood and which can lead to diabetic pre-coma. Symptoms of acidosis may include stomach pain, abnormal breathing and drowsiness (if severe). Before you start to use it: Risk of lactic acidosis [Product name] may cause a very rare, but very serious side effect called lactic acidosis, particularly if your kidneys are not working properly. The risk of developing lactic acidosis is also increased with uncontrolled diabetes, serious infections, prolonged fasting or alcohol intake, dehydration, liver problems and any medical conditions in which a part of the body has a reduced supply of oxygen (such as acute severe heart disease). If any of the above apply to you, talk to your doctor for further instructions. Stop taking [roduct name] for a short time if you have a condition that may be associated with dehydration (significant loss of body fluids) such as severe vomiting, diarrhoea, fever, exposure to heat or if you drink less fluid than normal. Talk to your doctor for further instructions. Stop taking [product name] and contact a doctor or the nearest hospital immediately if you experience some of the symptoms of lactic acidosis, as this condition may lead to coma. Symptoms of lactic acidosis include: • vomiting • stomach ache (abdominal pain) • muscle cramps • a general feeling of not being well with severe tiredness • difficulty in breathing Lactic acidosis is a medical emergency and must be treated in a hospital. During treatment with [product name], your doctor will check your kidney function at least once a year or more frequently if you are elderly and/or if you have worsening kidney function.

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	Reference: Directive No. 25, 2017. ***BPFK/PPP/07/25 (30) Jld. 1*** *Direktif Untuk Semua Produk Yang Mengandungi Metformin: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Penggunaan Dalam Kalangan Pesakit Yang Mempunyai Moderately Reduced Kidney Function Dan Pengukuhan Amaran Lactic Acidosis*
117.	**METHYL SALICYLATE** The following statements shall be included in the package inserts and product literature of topical preparations containing methyl salicylate ≥5%: **WARNINGS AND PRECAUTIONS** This product contains methyl salicylate and when applied or rub on to the skin, can be absorbed through the skin into the blood. For patients taking warfarin, excessive application on to the skin for muscle or joint pains may increase the chances of bleeding.
118.	**METHYLCARBOCYSTEINE (MECYSTEINE)** The following warning shall be included in the package inserts of products containing Methylcarbocysteine (Mecysteine): **CONTRAINDICATIONS** Contraindicated in children below two (2) years of age. **Reference: Directive No. 11, 2010.** ***Bil. (7) dlm. BPFK/PPP/01/03 Jilid 1*** *Kemaskini Kenyataan Amaran "Contraindicated In Children Under 2 Years Of Age" Yang Wajib Dimuatkan Pada Sisip Bungkusan Semua Produk Carbocysteine, Acetylcysteine dan Methylcarbocysteine (Mecysteine)*
119.	**METHYLPHENIDATE** The following boxed statement shall be included on the labels and in the package insert of products containing Methylphenidate HCl: **FOR SPECIALIST'S USE ONLY** The following statement shall be included in the package insert of products containing Methylphenidate: **WARNINGS AND PRECAUTIONS** **Priapism** Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products in both pediatric and adult patients. Priapism was not reported with drug initiation but developed after some time on the

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	drug, often subsequent to an increase in dose. Priapism has also appeared during a period of drug withdrawal (drug holidays or during discontinuation). Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention. **Reference: Directive No. 12, 2014.** ***Bil. (19) dlm.BPFK/PPP/07/25*** *Direktif Untuk Semua Produk Yang Mengandungi Methylphenidate: Amaran Berkaitan Risiko Priapism (Kesan Ereksi Yang Berpanjangan) Di Kalangan Lelaki*
120.	**METOCLOPRAMIDE** The following statements shall be included in the package inserts of products containing Metoclopramide: **DOSAGE** Total daily dose of metoclopramide, especially for children and young adults, should not normally exceed 0.5mg/kg body weight. **WARNINGS AND PRECAUTIONS** • Avoid doses exceeding 0.5mg/kg/day. • Extrapyramidal effects, especially dystonic reaction of metoclopramide are more likely to occur in children shortly after initiation of therapy, and usually with doses higher than 0.5mg per kg of body weight per day. The following route of products containing Metoclopramide shall update its package inserts according to Directive No. 17, 2014, ***Bil. (24) dlm.BPFK/PPP/07/25*** as below: **1) PARENTERAL ROUTE** • **Indication** • **Dose and Administration** • **Contraindication** • **Warnings and Precautions** **2) ORAL ROUTE (Tablet/ Syrup)** • **Indication** • **Dose and Administration** • **Contraindication** • **Warnings and Precautions** **3) RECTAL ROUTE (Suppository)** • **Indication**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	• **Dose and Administration** • **Contraindication** • **Warnings and Precautions** **Reference: Directive No. 17, 2014**. ***Bil. (24) dlm.BPFK/PPP/07/25*** *Direktif Untuk Semua Produk Metoclopramide: Memperketatkan Indikasi dan Mengehadkan Dos Penggunaan Berikutan Risiko Kesan Advers Neurologik*
121.	**METRONIDAZOLE (ALL PRODUCTS EXCEPT FOR EXTERNAL USE)** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products (except for external use) containing Metronidazole: **Package Insert** **a) Warnings and Precautions:** Cases of severe hepatotoxicity/ acute hepatic failure, including cases with a fatal outcome with very rapid onset after treatment initiation in patients with Cockayne syndrome have been reported with products containing metronidazole for systemic use. In this population, metronidazole should therefore be used after careful benefit-risk assessment and only if no alternative treatment is available. Liver function tests must be performed just prior to the start of therapy, throughout and after end of treatment until liver function is within normal ranges, or until the baseline values are reached. If the liver function tests become markedly elevated during treatment, the drug should be discontinued. Patients with Cockayne syndrome should be advised to immediately report any symptoms of potential liver injury to their physician and stop taking metronidazole. **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [product name]:** Inform your doctor if you are affected by Cockayne syndrome. Cases of severe liver toxicity/ acute liver failure in patients with Cockayne syndrome have been reported with products containing metronidazole. Stop taking [product name] and tell your doctor immediately if you develop: stomach pain, decreased appetite, nausea, vomiting, fever, unusual tiredness, yellowing of the skin and the whites of the eyes, dark-coloured urine, light or clay-coloured stools or itching.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Reference: Directive No. 18, 2017. ***BPFK/PPP/07/25 (23) Jld.1*** *Direktif Untuk Semua Produk Yang Mengandungi Metronidazole (Kecuali Produk Untuk Kegunaan Luar): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Amaran Berkaitan Risiko Hepatotoxicity Dalam Kalangan Pesakit Cockayne Syndrome*
122.	**MICONAZOLE** **1. Intravaginal preparations** The following boxed warning shall be included on the label and in the package insert of intravaginal preparations containing Miconazole: Sila dapatkan nasihat doktor atau ahli farmasi sebelum menggunakan keluaran ini jika anda mengambil ubat warfarin, iaitu sejenis ubat antipembekuan darah, kerana lebam/ pendarahan pada gusi/ hidung boleh berlaku secara spontan. (Please consult your physician/ pharmacist before using this product if you are on the anticoagulant medicine warfarin, because bleeding from nose/ gums or bruising may accur spontaneously). **Reference:** ***Bil. (45) dlm. BPFK/02/5/1.2*** *Keputusan Mesyuarat Pihak berkuasa Kawalan Dadah (PBKD) ke 122 Berhubung Amaran Berkaitan Interaksi Ubat Bagi Semua Keluaran Antifungal Intravaginal Yang Mengandungi Miconazole* **2. Oral gel preparations** The following statements shall be included in the package insert and RiMUP of oral gel preparations containing Miconazole: **Package Insert** **a) Contraindications** Use of miconazole oral gel in combination with the following drug that is subjected to metabolism by CYP2C9 (see Interactions): • Warfarin **b) Interactions** Miconazole can inhibit the metabolism of drugs metabolized by the CYP2C9 enzyme system. This can result in an increase and/or prolongation of their effects, including adverse effects.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Miconazole oral gel is contraindicated with the co-administration of the following drug that is subjected to metabolism by CYP2C9 (see Contraindications): • Warfarin **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [product name]** When you must not use it Do not use [product name] if you are on warfarin therapy. **3. Preparations other than oral gel** The following statements shall be included in the package insert and RiMUP of preparations (other than oral gel) containing Miconazole: **Package Insert** **a) Warnings and Precautions** In patients on warfarin, caution should be exercised and the anticoagulant effect should be monitored (see Interactions). **b) Interactions** Miconazole administered systemically is known to inhibit CYP2C9 enzyme system. Due to the limited systemic availability after topical application, clinically relevant interactions occur very rarely. In patients on warfarin which is subjected to metabolism by CYP2C9, caution should be exercised and the anticoagulant effect should be monitored (see Warnings and Precautions). **Consumer Medication Information Leaflet (RiMUP)** **a) Before You Use [Product Name]** Before you start to use it You must tell your doctor if you: • are on warfarin therapy **Reference: Directive No. 10, 2017.** ***BPFK/PPP/07/25 (15) Jld. 1*** *Direktif Untuk Semua Produk Yang Mengandungi Miconazole: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Interaksi Ubat*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
123.	**MIDAZOLAM** The following statements shall be included in the package inserts of IV preparations containing Midazolam: **WARNINGS AND PRECAUTIONS** IV Midazolam has been associated with severe respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy resulted. IV Midazolam should be used only in hospital or ambulatory care settings that provide for continuous monitoring of respiratory and cardiac functions. Assure immediate availability of resuscitative drugs, equipments, appropriate antidote and personnel trained in their use. Dosage of IV Midazolam must be individualized for each patient. Lower doses are usually required for elderly, debilitated or higher risk surgical patients. When Midazolam is administered intravenously for conscious sedation, it should be injected slowly (over at least 2 minutes); it should not be administered by rapid or single bolus IV injection because of respiratory depression and/or arrest, especially in elderly or debilitated patients. The initial dose may be as little as 1mg, but should not exceed 2.5mg in a normal healthy adult; administer over at least 2 minutes and allow additional 2 or more minutes to fully evaluate sedative effect. If further titration is necessary, use small increments to the appropriate level of sedation, allowing an additional 2 or more minutes after each increment to fully evaluate sedative effect. See Dosage and Administration for complete dosing information.
124.	**MINOCYCLINE** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing Minocycline: **Package Insert** **a) Warnings and Precautions:** Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) including fatal cases have been reported with minocycline use. DRESS, which often occurs several weeks after initiation of treatment, consists of a combination of three or more of the following: cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, lymphadenopathy, and one or more systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and pericarditis. Discontinue minocycline if DRESS is suspected.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	b) Adverse Effects/ Undesirable Effects: Skin and subcutaneous tissue disorders: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Side Effects:** Stop taking [product name] and contact your doctor immediately if you experience any of the following: • Serious allergic reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). DRESS appears initially as flu-like symptoms with a rash on the face and then with an extended rash, high temperature and enlarged lymph nodes. **Reference: Directive No. 6, 2018.** ***BPFK/PPP/07/25 (6) Jld. 2*** *Direktif Untuk Semua Produk Yang Mengandungi Minocycline: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS)*
125.	**MINOXIDIL** The label and the package insert shall include the following statement: **To be supplied only on the prescription of a registered medical practitioner.** ***<u>Note:</u>*** The statement is <u>exempted for external use preparation</u> containing not more than 5% of Minoxidil; its salts; its derivatives *(Please refer to the latest Poison List: Preparations for external use containing not more than 5% of Minoxidil; its salts; its derivatives, which is under Group C)*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
126.	**MIRTAZAPINE** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing Mirtazapine; **Package Insert** **a) Adverse Effects/ Undesirable Effects:** Nervous system disorders Frequency 'common': Amnesia Skin and subcutaneous tissue disorders Frequency 'not known': Drug reaction with eosinophilia and systemic symptoms (DRESS) **Consumer Medication Information Leaflet (RiMUP)** **a) Side effects:** Frequency 'common': Memory problems Frequency 'not known': Serious allergic reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). DRESS appears initially as flu-like symptoms with a rash on the face and then with an extended rash, high temperature and enlarged lymph nodes. **Reference: Directive No. 12, 2021**. *NPRA.600-1/9/13(22) Direktif Untuk Semua Produk Yang Mengandungi Mirtazapine: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Amnesia dan Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS)*
127.	**MOMORDICA CHARANTIA** For product containing Momordica Charantia, please state: - **"Shall not be used in pregnant and breast-feeding women."** - **"Be sure to tell your pharmacist, doctor, or other healthcare providers about any other supplements you are taking. There may be a potential for interactions or side effects."**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
128.	**MONTELUKAST** The following statement shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products that contains Montelukast: **Package Insert** **a) Adverse Effects/Undesirable Effects:** Postmarketing Experience Blood and lymphatic system disorders: thrombocytopenia Psychiatric disorders: obsessive-compulsive symptoms **Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects:** Tell your healthcare provider right away if you notice any of the following behavior and mood-related changes: • Obsessive-compulsive symptoms **References:** **Directive No. 6, 2015.** ***Bil. (31) dlm.BPFK/PPP/07/25*** *Direktif Untuk Semua Produk Yang Mengandungi Montelukast: Pengemaskinian Sisip Bungkusan Dengan Maklumat Kesan Advers Berkaitan Thrombocytopenia* **Directive No. 8, 2019.** ***BPFK/PPP/07/25 (8) Jld.3*** *Direktif Untuk Semua Produk Yang Mengandungi Montelukast: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Penambahan Maklumat Keselamatan Berkaitan Risiko Obsessive-Compulsive Symptoms*
129.	**MYCOPHENOLATE (MYCOPHENOLATE MOFETIL AND MYCOPHENOLIC ACID)** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing mycophenolate (mycophenolate mofetil and mycophenolic acid): **Package Insert** **CONTRAINDICATIONS** • [Product name] is contraindicated during pregnancy due to its mutagenic and teratogenic potential (see Use in Special Populations: Pregnancy). • [Product name] is contraindicated in women of childbearing potential not using highly effective contraceptive methods (see Use in Special Populations: Pregnancy). • [Product name] is contraindicated in women who are breastfeeding (see Use in Special Populations: Breastfeeding).

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	USE IN SPECIAL POPULATIONS **Pregnancy** [Product name] is contraindicated during pregnancy and in women of childbearing potential not using highly effective contraceptive methods. (see Contraindications). Before the start of treatment, female and male patients of reproductive potential must be made aware of the increased risk of pregnancy loss and congenital malformations and must be counseled regarding pregnancy prevention, and planning. Prior to starting therapy with [product name], female patients of childbearing potential must have **two negative serum or urine pregnancy tests** with a sensitivity of at least 25 mIU/mL; The second test should be performed 8-10 days after the first one and immediately before starting [product name]. Repeat pregnancy tests should be performed during routine follow-up visits. Results of all pregnancy tests should be discussed with the patient. Patients should be instructed to consult their physician immediately should they become pregnant. Due to the mutagenic and teratogenic potential of mycophenolate, **women of child bearing potential** should use **two reliable forms of contraception** simultaneously, including at least one highly effective method, before beginning mycophenolate therapy, during therapy, and for six weeks following discontinuation of therapy, unless abstinence is the chosen method of contraception. **Sexually active men** are recommended to use condoms during treatment and for at least 90 days after cessation of treatment. Condom use applies for both reproductively competent and vasectomised men, because the risks associated with the transfer of seminal fluid also apply to men who have had a vasectomy. In addition, **female partners of male patients** are recommended to use highly effective during treatment and for total of 90 days after the last dose of [product name]. Congenital malformations, including multiple malformations have been reported post-marketing in children of patients exposed to mycophenolate in combination with other immunosuppressants during pregnancy. The following malformations were most frequently reported: • Facial malformations such as cleft lip, cleft palate, micrognathia and hypertelorism of the orbits; • Abnormalities of the ear (e.g. abnormally formed or absent external/middle ear) and eye (e.g. coloboma, microphthalmos); • Malformations of the fingers (e.g. polydactyly, syndactyly, brachydactyly); • Cardiac abnormalities such as atrial and ventricular septal defects; • Oesophageal malformations (e.g. oesophageal atresia); • Nervous system malformations (such as spina bifida).

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	In the medical literature, malformations in children from mycophenolate-exposed pregnancies have been reported in 23% to 27% of live births. For comparison, the risk of malformations is estimated at approximately 2% of live births in the overall population and at approximately 4% to 5 % in solid organ transplant patients treated with immunosuppressants other than mycophenolate. Cases of spontaneous abortions have also been reported in patients exposed to mycophenolate, mainly in the first trimester. In the medical literature, the risk has been reported at 45% to 49% following mycophenolate exposure, compared to a reported rate between 12 and 33% in solid organ transplant patients treated with other immunosuppressants. Studies in animals have shown reproductive toxicity. **Breastfeeding** [Product name] is contraindicated during breastfeeding due to the potential for serious adverse reactions in nursing infants (see Contraindications). Studies in rats have shown mycophenolate to be excreted in milk. It is not known whether this medicine is excreted in human milk. **ADVERSE EFFECTS/ UNDESIRABLE EFFECTS** General disorders and administration site conditions: (uncommon) de novo purine synthesis inhibitors-associated acute inflammatory syndrome <u>General disorders and administration site conditions</u> De novo purine synthesis inhibitors-associated acute inflammatory syndrome has been described from post-marketing experience as a paradoxical proinflammatory reaction associated with mycophenolate mofetil and mycophenolic acid, characterised by fever, arthralgia, arthritis, muscle pain and elevated inflammatory markers. Literature case reports showed rapid improvement following discontinuation of the medicinal product. **Post-marketing experience:** **Congenital Disorders** Congenital malformations have been reported post-marketing in children of patients exposed to mycophenolate in combination with other immunosuppressants during pregnancy (see Use in Pregnancy). **Pregnancy, Puerperium and Perinatal Conditions** Cases of spontaneous abortions mainly in the first trimester in patients exposed to mycophenolate have been reported (see Use in Pregnancy).

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Consumer Medication Information Leaflet (RiMUP) **SIDE EFFECTS** Tell your doctor or pharmacist if you notice any of the following: fever, joint pain and muscle pain. **References**: **Directive No. 6, 2016.** ***BPFK/PPP/07/25 (37)*** *Direktif Untuk Semua Produk Yang Mengandungi Mycophenolate (Mycophenolate Mofetil dan Mycophenolic Acid): Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Risiko Kesan Teratogenik* **Directive No. 19, 2021**. ***NPRA.600-1/9/13(29)*** *Direktif Untuk Semua Produk Yang Mengandungi Mycophenolate (Mycophenolate Mofetil dan Mycophenolic Acid): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko De Novo Purine Synthesis Inhibitors-Associated Acute Inflammatory Syndrome*
130.	**NEVIRAPINE** The following statement shall be included in the package insert of products containing Nevirapine: Addition of this statement at approved Indication: "Avoid usage of Nevirapine in patient with CD4+cell count greater than 250cells/mm3". **Reference:** ***Bil. (43) dlm. BPFK/02/5/1.3*** *Pendaftaran Produk Yang Mengandungi Nevirapine*
131.	**NIFEDIPINE** The following statement shall be included in the package inserts of "short acting" Nifedipine products: **WARNINGS AND PRECAUTIONS** Several well documented studies have described profound hypotension, myocardial infarction and death when immediate release nifedipine capsules are used sublingually for acute reduction of blood pressure. **DOSAGE** • Lower doses may be required in elderly patients as a result of reduced drug clearance. • For hypertension, the dose used should not exceed 60mg daily.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
132.	**NITRATES** The following statements shall be included in the package inserts of all "**NITRATES FOR STABLE ANGINA PECTORIS**": • An appropriate statement concerning the development of tolerance (under **precaution** section). A suggested statement would be as follows: 'Development of tolerance may occur with all forms of nitrate therapy particularly with the long acting preparations that maintain continuously high plasma nitrate concentration'. • An appropriate recommendation on dosage regimens. The recommended dosage regimens should be one that is able to provide a low-nitrate period or a nitrate-free period of 8-12 hours every 24 hours to prevent the development of tolerance and thus maintain the antianginal effects.
133.	**NORADRENALINE** The following statements shall be included in the package insert of products containing noradrenaline; **Package Insert** **a) Adverse Effects/Undesirable Effects:** Cardiac disorders Frequency 'not known': stress cardiomyopathy **Reference: Directive No. 5, 2019.** ***BPFK/PPP/07/25 (5) Jld.3*** *Direktif Untuk Semua Produk Yang Mengandungi Noradrenaline: Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Stress Cardiomyopathy*
134.	**NORFLOXACIN** The following statement shall be included in the package inserts of products containing Norfloxacin: **PRECAUTION** i. Should not be used in children or pregnant women ii. Phototoxicity may occur

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
135.	**NORMAL GLOBULIN** **INTRAMUSCULAR (IM)** The following statement shall be included in the package inserts of Normal globulin IM preparations: **WARNINGS AND PRECAUTIONS** Do not administer this preparation intravenously because of potential for serious hypersensitivity reactions.
136.	**NOSCAPINE** 1. The following **contraindication** shall be included on the labels of products containing Noscapine: **Contraindicated in Women of Child-bearing Potential** 2. The following statement shall be included in the package inserts of products containing Noscapine: **WARNINGS AND PRECAUTIONS** Experimental data now suggests that noscapine may exhibit a mutagenic effect in vitro. Because of the possible consequent risk to the developing foetus, the products containing noscapine is contraindicated in women of child bearing potential, therefore pregnancy should be excluded before treatment, and effective contraception maintained throughout treatment with such products. **PRECAUTION** In view of potential mutagenicity shown in vitro, potential risks should be balanced against anticipated benefits when treating children and neonates.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
137.	**NONSTEROIDAL ANTI-INFLAMMATORY DRUG (NSAID)** The following statement shall be included in the package insert of products containing NSAID including COX-2 Inhibitors: **WARNINGS AND PRECAUTIONS** Risk of GI Ulceration, Bleeding and Perforation with NSAID Serious GI toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated with NSAID therapy. Although minor upper GI problems (e.g. dyspepsia) are common, usually developing early in therapy, prescribers should remain alert for ulceration and bleeding in patients treated with NSAIDs even in the absence of previous GI tract symptoms. Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Patients with prior history of serious GI events and other risk factors associated with peptic ulcer disease (e.g. alcoholism, smoking, and corticosteroid therapy) are at increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less than other individuals and account for most spontaneous reports for fatal GI events.
138.	**OLANZAPINE** The following statements shall be included in the package insert and RiMUP of products containing Olanzapine: **Package Insert** **a) Warnings and Precautions**: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported with olanzapine exposure. DRESS consists of a combination of three or more of the following: cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, lymphadenopathy and one or more systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and pericarditis. Discontinue olanzapine if DRESS is suspected. **b) Adverse Effects/ Undesirable Effects**: **Skin and subcutaneous tissue disorders** Very rare: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Consumer Medication Information Leaflet (RiMUP) **a) Side Effects**: Very rare: Serious allergic reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). DRESS appears initially as flu-like symptoms with a rash on the face and then with an extended rash, high temperature, enlarged lymph nodes, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia). **Reference: Directive No. 19, 2016.** ***BPFK/PPP/07/25 (5) Jld.1*** *Direktif Bagi Semua Produk Yang Mengandungi Olanzapine Dengan Maklumat Keselamatan Berkaitan Kesan Advers Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS)*
139.	**ONDANSETRON** The following statements shall be included in the package inserts and Consumer Medication Information Leaflet (RiMUP) for products containing Ondansetron; **Package Insert** **a) Dosage And Administration:** **CHEMOTHERAPY AND RADIOTHERAPY INDUCED NAUSEA AND VOMITING (CINV AND RINV)** **CINV and RINV in Adults** …. IV doses greater than 8 mg and up to a maximum of 16 mg must be diluted in 50 mL to 100 mL of 0.9% Sodium Chloride Injection or 5% Dextrose Injection before administration and infused over not less than 15 minutes. …. **CINV and RINV in Elderly** Ondansetron is well tolerated by patients over 65 years of age. In patients 65 years of age or older, all IV doses should be diluted and infused over 15 minutes and, if repeated, given no less than 4 hours apart. In patients 65 to 74 years of age, the initial IV dose of ondansetron 8 mg or 16 mg, infused over 15 minutes, may be followed by 2 doses of 8 mg infused over 15 minutes and given no less than 4 hours apart.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	In patients 75 years of age or older, the initial IV dose of ondansetron should not exceed 8 mg infused over 15 minutes. The initial dose of 8 mg may be followed by 2 doses of 8 mg, infused over 15 minutes and given no less than 4 hours apart. *Reference: Zofran™ Injection package insert (June 2014 version)* **b) Pregnancy and Lactation:** Pregnancy The use of ondansetron in pregnancy is not recommended. In human epidemiological studies, an increase in orofacial clefts was observed in infants of women administered ondansetron during the first trimester of pregnancy. Regarding cardiac malformations, the epidemiological studies showed conflicting results. Three epidemiological studies in the US assessed the risk of specific congenital anomalies, including orofacial clefts and cardiac malformations in offspring born to mothers exposed to ondansetron during the first trimester of pregnancy. • One cohort study with 88,467 pregnancies exposed to ondansetron showed an increased risk of oral clefts (3 additional cases per 10,000 women treated, adjusted relative risk (RR), 1.24 (95% CI 1.03-1.48)) without an apparent increase in risk of cardiac malformations. A separately published subgroup analysis of 23,877 pregnancies exposed to intravenous ondansetron did not find an increased risk of either oral clefts or cardiac malformations. • One case-control study using population-based birth defect registries with 23,200 cases across two datasets showed an increased risk of cleft palate in one dataset and no increased risk in the other dataset. There was no increased risk of cardiac malformations in this study. • The second cohort study with 3,733 pregnancies exposed to ondansetron found an increased risk of ventricular septal defect, adjusted RR 1.7 (95%CI 1.0-2.9), but no statistically significant increase in risk of cardiac malformations. Reproductive studies in rats and rabbits did not show evidence of harm to the fetus. Pregnancy status should be verified for females of reproductive potential prior to starting the treatment with [product name]. Females of reproductive potential should be advised that it is possible that [product name] can cause harm to the developing fetus. Sexually active females of reproductive potential are recommended to use effective contraception (methods that result in less than 1 % pregnancy rates) when using [product name] during

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	the treatment and for two days after stopping treatment with [product name]. **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Before you use [product name]:** [Product name] is not recommended for use during pregnancy. • Tell your doctor if you are pregnant or planning to become pregnant. [Product name] may harm your unborn baby. • If you do become pregnant during treatment with [product name], tell your doctor. If you are a woman of childbearing age, your doctor will check if you are pregnant and perform a pregnancy test if necessary before starting treatment with [product name]. If you may become pregnant, you should use effective birth control during treatment and for at least 2 days after stopping [product name]. Ask your doctor about options of effective birth control. **Reference: Directive No. 5, 2021.** ***NPRA.600-1/9/13(15)*** *Direktif Untuk Semua Produk Yang Mengandungi Ondansetron: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Kecacatan Kelahiran (Birth Defects) Susulan Penggunaan Ketika Hamil*
140.	**OPIOID** The following statements shall be <u>included in the package insert and RiMUP</u> of pharmaceutical products containing opioid: **<u>Package Insert</u>** **a) Warnings and Precautions:** 1. <u>Risks from Concomitant Use with Benzodiazepines</u> Profound sedation, respiratory depression, coma, and death may result from the concomitant use of [product name] with benzodiazepines. Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. If the decision is made to newly prescribe a benzodiazepine and an opioid together, prescribe the lowest effective dosages and minimum durations of concomitant use.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	If the decision is made to prescribe a benzodiazepine in a patient already receiving an opioid, prescribe a lower initial dose of the benzodiazepine than indicated in the absence of an opioid, and titrate based on clinical response. If the decision is made to prescribe an opioid in a patient already taking a benzodiazepine, prescribe a lower initial dose of the opioid, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when [product name] is used with benzodiazepines. Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of benzodiazepines (See Drug Interactions). 2. <u>Serotonin Syndrome with Concomitant Use of Serotonergic Drugs</u> Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concurrent use of [product name] with serotonergic drugs (See Interactions with Other Medicaments). This may occur within the recommended dosage range. Serotonin syndrome symptoms may include mental-status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea) and can be fatal (See Interactions with Other Medicaments). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue [product name] if serotonin syndrome is suspected. 3. <u>Adrenal Insufficiency</u> Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, decreased appetite, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement dosing of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	4. Sexual Function/Reproduction Long term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (See Postmarketing Experience) **b) Adverse Effects/ Undesirable Effects:** Postmarketing Experience: Serotonin syndrome (See Warnings and Precautions) Adrenal insufficiency (See Warnings and Precautions) Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids. Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation. Infertility: Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible. **c) Interactions:** 1. Benzodiazepines Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death. The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at μ-receptors, and benzodiazepines interact at $GABA_A$ sites. When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see Warnings and Precautions). Limit dosage and duration of concomitant use of benzodiazepines and opioids,

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	and follow patients closely for respiratory depression and sedation. 2. Serotonergic Drugs The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue [product name] if serotonin syndrome is suspected. Examples of serotonergic drugs are selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g. mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) (See Warnings and Precautions). **Consumer Medication Information Leaflet (RiMUP)** **a) While you are using it:** Things to be careful of: - Serotonin syndrome: [Product name] may cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. If you have some or all of these symptoms: feeling confused, feeling restless, sweating, shaking, shivering, hallucinations, sudden jerks in your muscles or a fast heartbeat, seek medical attention immediately. - Adrenal insufficiency: Long-term use of [product name] may cause adrenal insufficiency, a potentially life-threatening condition that may present with non-specific symptoms and signs such as nausea, vomiting, decreased appetite, fatigue, weakness, dizziness, and low blood pressure. Seek medical attention if you experience a constellation of these symptoms. - Infertility: Long-term use of [product name] may cause reduced fertility. It is not known whether these effects on fertility are reversible. **b) Taking other medicines:** Taking [product name] with a benzodiazepine (medicine used as sedatives or to treat anxiety) can depress your central nervous system. Inform your doctor if you are currently taking any benzodiazepine. Seek medical attention immediately if you or the person taking this medication experience(s) symptoms of unusual dizziness or lightheadedness, extreme sleepiness, slowed or difficult breathing, or unresponsiveness.

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	References: **Directive No. 23, 2017.** ***BPFK/PPP/07/25 (28) Jld. 1*** *Direktif Untuk Semua Produk Yang Mengandungi Opioid dan Benzodiazepin: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Interaksi Ubat* **Directive No. 27, 2017.** ***BPFK/PPP/07/25 (32) Jld. 1*** *Direktif Untuk Semua Produk Yang Mengandungi Opioid: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Kesan Advers Serotonin Syndrome Kesan Daripada Interaksi Dengan Serotonergic Drugs dan Risiko Kesan Advers Adrenal Insufficiency dan Androgen Deficiency Akibat Penggunaan Jangka Panjang*
141.	**OSELTAMIVIR** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing Oseltamivir; **Package Insert** **a) Adverse Effects/Undesirable Effects:** Blood and lymphatic system disorders Frequency 'Rare' : Thrombocytopenia **Consumer Medication Information Leaflet (RiMUP)** **a) Side effects**: Rare side effects: - thrombocytopenia (low platelet count) **Reference: Directive No. 6, 2021.** ***NPRA.600-1/9/13 (16)*** *Direktif Untuk Semua Produk Yang Mengandungi Oseltamivir: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Thrombocytopenia*
142.	**PALIPERIDONE** The following statement shall be included in the package inserts of products containing Paliperidone: **Warnings and Precautions** **Intraoperative Floppy Iris Syndrome** Intraoperative floppy iris syndrome (IFIS) has been observed during cataract surgery in patients treated with medicines with alpha1a-adrenergic antagonist effect, including risperidone. IFIS may increase the risk of eye complications

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	during and after the operation. Current or past use of medicines with alpha1a-adrenergic antagonist effect should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping alpha1 blocking therapy prior to cataract surgery has not been established and must be weighed against the risk of stopping the antipsychotic therapy. **Adverse Effects / Undesirable Effects** **Postmarketing Data** Eye Disorders Frequency: Not known – Floppy iris syndrome (intraoperative) **Reference:** ***Bil. (17) dlm.BPFK/PPP/01/03 Jld.3*** *Pekeliling Untuk Mengemaskini Sisip Bungkusan Semula Produk Yang Mengandungi Risperidone Atau Paliperidone Dengan Amaran Berkaitan Risiko Intraoperative Floppy Iris Syndrome (IFIS) Pada Pesakit Yang Menjalani Pembedahan Katarak*
143.	**PARACETAMOL** The following statement shall be included on the labels, package inserts and RiMUP of ALL products containing Paracetamol: **WARNING** This preparation contains PARACETAMOL. Do not take any other paracetamol containing medicines at the same time. • **Allergy alert:** Paracetamol may cause severe skin reactions. Symptoms may include skin reddening, blisters or rash. These could be signs of a serious condition. If these reactions occur, stop use and seek medical assistance right away. **Package Insert** **ADVERSE EFFECTS/ UNDESIRABLE EFFECTS** • Cutaneous hypersensitivity reactions including skin rashes, angioedema, Stevens Johnson Syndrome/Toxic Epidermal Necrolysis have been reported. **Reference: Directive No. 5, 2015.** ***Bil. (29) dlm.BPFK/PPP/07/25*** *Direktif Untuk Produk Yang Mengandungi Paracetamol, Termasuk Produk Kombinasi: Pengemaskinian Label, Sisip Bungkusan, dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Amaran Berkaitan Kesan Advers Serius Pada Kulit*

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144.	**PARACETAMOL WITH CAFFEINE IN COMBINATION** The following statement shall be included on the labels and in the package inserts and RiMUP of products containing Paracetamol with Caffeine in combination: **WARNING** • Avoid other caffeine containing products. Too much caffeine may cause rapid heart rate, nervousness or sleeplessness. • Ask a doctor or pharmacist before use if you have high blood pressure, glaucoma, or overactive bladder syndrome. • **DO NOT exceed 8 tablets in 24 hours**. • **DO NOT** take more than the recommended dose unless advised by your doctor. Use the smallest effective dose. Taking more than the maximum daily dose may cause **severe or possibly fatal liver damage.** • **DO NOT** use with other drugs containing **paracetamol.** • **NOT recommended for children under 12 years** **Package Insert** **ADVERSE EFFECTS/ UNDESIRABLE EFFECTS** • Cutaneous hypersensitivity reactions including skin rashes, angioedema, Stevens Johnson Syndrome/Toxic Epidermal Necrolysis have been reported. **Reference: Directive No. 5, 2015.** ***Bil. (29) dlm.BPFK/PPP/07/25*** *Direktif Untuk Produk Yang Mengandungi Paracetamol, Termasuk Produk Kombinasi: Pengemaskinian Label, Sisip Bungkusan, dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Amaran Berkaitan Kesan Advers Serius Pada Kulit*

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145.	**PARENTERAL NUTRITION CONTAINING AMINO ACIDS AND/OR LIPIDS (INDICATED FOR USE IN PEDIATRIC POPULATION AGED UNDER 2 YEARS)** The following statements shall be included in the package insert of parenteral nutrition products containing amino acids and/or lipids (indicated for use in pediatric population aged under 2 years); **Package Insert** **a) Dosage and Administration:** When used in neonates and children below 2 years, the solution (in bags and administration sets) should be protected from light exposure until administration is completed (See Section **Warnings and Precautions**). **b) Warnings and Precautions:** Light exposure of solutions for intravenous parenteral nutrition, especially after admixture with trace elements and/or vitamins, may have adverse effects on clinical outcome in neonates, due to generation of peroxides and other degradation products. When used in neonates and children below 2 years, <product name> should be protected from ambient light until administration is completed (See Section **Dosage and Administration**). **Reference: Directive No. 15, 2020.** ***NPRA.600-1/9/13 (6)*** *Direktif Untuk Semua Produk Parenteral Nutrition Yang Mengandungi Asid Amino Dan/Atau Lipid (Yang Indikasinya Termasuk Untuk Kegunaan Dalam Kalangan Golongan Pediatrik Di Bawah Usia Dua Tahun): Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Kesan Advers (Adverse Outcomes) Akibat Pendedahan Produk Kepada Cahaya Semasa Administrasi*
146.	**PEGFILGRASTIM** The following statement shall be included in the package inserts of ALL biosimilar products containing PEGFILGRASTIM **WARNINGS AND PRECAUTIONS** Capillary leak syndrome has been reported after granulocyte-colony stimulating factor administration and is characterised by hypotension, hypoalbuminaemia, oedema and hemoconcentration. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care. Aortitis has been reported after G-CSF administration in healthy subjects and in cancer patients. The symptoms experienced included fever, abdominal pain, malaise, back pain and increased inflammatory markers (e.g. C-reactive protein and white blood cell count). In most cases aortitis was diagnosed by CT scan and generally resolved after withdrawal of G-CSF.

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	ADVERSE EFFECTS/ UNDESIRABLE EFFECTS Clinical Trials **In Cancer Patients** Capillary Leak Syndrome, which can be life-threatening if treatment is delayed, has been reported uncommonly (≥1/1000 to < 1/100) in cancer patients undergoing chemotherapy following administration of granulocyte colony stimulating factors. **In Normal Donors undergoing peripheral blood progenitor cell mobilization** Capillary Leak Syndrome, which can be life-threatening if treatment is delayed, has been reported in healthy donors undergoing peripheral blood progenitor cell mobilization following administration of granulocyte colony stimulating factors. Post Marketing **Vascular disorders** Cases of capillary leak syndrome have been reported in the post marketing setting with granulocyte colony stimulating factor use. These have generally occurred in patients with advanced malignant diseases, sepsis, taking multiple chemotherapy medications or undergoing apheresis. Frequency "rare": Aortitis **References:** **Directive No. 13, 2014.** ***Bil. (20) dlm. BPFK/PPP/07/25*** *Direktif Untuk Semua Produk Yang Mengandungi Filgrastim dan Pegfilgrastim: Amaran Berkaitan Risiko Capillary Leak Syndrome (CLS) Bagi Pesakit Kanser dan Healthy Donor (Filgrastim) dan Bagi Pesakit Kanser (Pegfilgrastim)* **Directive No. 30, 2018.** ***Bil. (30) dlm. BPFK/PPP/07/25*** *Direktif Untuk Semua Produk Yang Mengandungi Filgrastim, Pegfilgrastim dan Lenograstim: Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Aortitis*
147.	***PELARGONIUM SIDOIDES*** The following warning shall be included on the labels and in the package inserts of products containing *Pelargonium Sidoides*: **WARNING** In very rare cases, *pelargonium sidoides* may cause hypersensitivity reactions.
148.	**PEMETREXED** The following statements shall be included in the package insert for products containing pemetrexed: **a) Warnings and Precautions:**

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	Nephrogenic diabetes insipidus and renal tubular necrosis were also reported in post marketing setting with pemetrexed alone or with other chemotherapeutic agents. Most of these events resolved after pemetrexed withdrawal. Patients should be regularly monitored for acute tubular necrosis, decreased renal function and signs and symptoms of nephrogenic diabetes insipidus (e.g. hypernatraemia). **b) Adverse Effects/Undesirable Effects:** Nephrogenic diabetes insipidus and renal tubular necrosis have been reported in post marketing setting with an unknown frequency. **Reference: Directive No. 29, 2018.** ***BPFK/PPP/07/25 (29) Jld.2*** *Direktif Untuk Semua Produk Yang Yang Mengandungi Pemetrexed: Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Nephrogenic Diabetes Insipidus dan Renal Tubular Necrosis*
149.	**PENICILLIN** The following statement shall be included on the labels of products containing penicillin: **'Not to be used in patients with known hypersensitivity to Penicillin'**
150.	**PHENIRAMINE** The following statement shall be included on the label and in the package inserts of liquid oral products containing Pheniramine: **WARNING** When used for treatment of cough and cold: (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. **Reference:** ***Bil. (34) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*

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151.	**PHENYLEPHRINE** The following statement shall be included on the labels and in the package insert of liquid oral products containing Phenylephrine: **WARNING** When used for treatment of cough and cold: (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. **Reference:** ***Bil. (34) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*
152.	**PIROXICAM (SYSTEMIC)** The following additional information shall be included in the package inserts of products containing Piroxicam (systemic): **WARNINGS AND PRECAUTIONS** • Treatment should always be initiated by a physician experienced in the treatment of rheumatic diseases. • Use the lowest dose (no more than 20mg per day) and for the shortest duration possible. Treatment should be reviewed after 14 days. • Always consider prescribing a gastro-protective agent. **CONTRAINDICATIONS** • Piroxicam should not be prescribed to patient who is more likely to develop side effects, such as those with a history of gastro-intestinal disorders associated with bleeding, or those who have had skin reactions to other medicines. • Piroxicam should not be prescribed in association with any other NSAID or an anticoagulant. **Reference:** ***Bil. (80) dlm. BPFK/02/5/1.3*** *Menghadkan Indikasi bagi Produk untuk Kegunaan 'Systemic' yang Mengandungi Piroxicam kepada 'For the symptomatic relief of pain and inflammation in patients with osteoarthritis, rheumatoid arthritis and ankylosing spondylitis' dan Tambahan Amaran Dan Kontraindikasi Terkini Pada Sisip Bungkusan*

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153.	**PRAVASTATIN** The following additional information shall be included in the package insert of products containing Pravastatin. **DOSAGE AND ADMINISTRATION** Dosage in Patients Taking Cyclosporine In patients taking cyclosporine, with or without other immunosuppressive drugs, concomitantly with [Product Name], therapy should be initiated with 10mg/day and titration to higher doses should be performed with caution. Most patients treated with this combination received a maximum pravastatin dose of 20mg/day. **WARNINGS AND PRECAUTIONS** Skeletal Muscle Effects The use of fibrates alone may occasionally be associated with myopathy. The benefit of further alterations in lipid levels by the combined use of [Product Name] with fibrates should be carefully weighed against the potential risks of this combination. Cases of myopathy, including rhabdomyolysis, have been reported with pravastatin co-administered with colchicine, and caution should be exercised when prescribing pravastatin with colchicine. Pravastatin must not be co-administered with systemic fusidic acid. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. Pravastatin therapy may be re-introduced seven days after the last dose of fusidic acid. **INTERACTIONS** Concomitant Therapy with Other Lipid Metabolism Regulators: Based on post-marketing surveillance, gemfibrozil, fenofibrate, other fibrates and lipid lowering doses of niacin (nicotinic acid) may increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone. Therefore, combined drug therapy should be approached with caution. Gemfibrozil and nicotinic acid: Gemfibrozil and nicotinic acid do not statistically

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	significantly affect the bioavailability of pravastatin. However, in a limited size clinical trial, a trend toward CK elevations and musculoskeletal symptoms was seen in patients treated concurrently with pravastatin and gemfibrozil. Myopathy, including rhabdomyolysis, has occurred in patients who were receiving coadministration of HMG-CoA reductase inhibitors with fibric acid derivatives and niacin, particularly in subjects with pre-existing renal insufficiency. Cyclosporine: In a multicentre study, the AUC values of pravastatin were shown to be five-fold higher in the presence of cyclosporine. There was no accumulation of pravastatin after multiple doses Clarithromycin, colchicine: The risk of myopathy/rhabdomyolysis is increased with concomitant administration of clarithromycin or colchicine with pravastatin. Fusidic acid: The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of pravastatin with systemic fusidic acid. Co-administration of this combination may cause increased plasma concentrations of both agents. The mechanism of this interaction (whether it is pharmacodynamics or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. If treatment with fusidic acid is necessary, pravastatin treatment should be discontinued throughout the duration of the fusidic acid treatment. **Reference: Directive No. 8, 2014.** ***Bil. (15) dlm. BPFK/PPP/07/25*** *Direktif Untuk Semua Produk Pravastatin: Mengehadkan Dos Penggunaan Pravastatin Untuk Mengurangkan Risiko Kecederaan Otot*
154.	**PREDNISONE AND PREDNISOLONE (EXCEPT TOPICAL PREPARATIONS)** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing Prednisone dan Prednisolone (except topical preparations); **Package Insert** **a) Warnings and Precautions:** Scleroderma renal crisis Caution is required in patients with systemic sclerosis because of an increased incidence of (possibly fatal) scleroderma renal crisis with hypertension and decreased urinary output observed with a daily dose of 15 mg or more prednisolone.

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	Consumer Medication Information Leaflet (RiMUP) **a) Before you start to use it:** Talk to your doctor before taking [product name], if you have: Systemic sclerosis (an autoimmune disorder). Taking daily doses of 15 mg or more may increase the risk of a serious complication called scleroderma renal crisis which may cause your blood pressure to increase and reduce urination. **Reference: Directive No. 17, 2018.** ***BPFK/PPP/07/25 (17) Jld. 2*** *Direktif Untuk Semua Produk Yang Mengandungi Prednisone dan Prednisolone (Kecuali Persediaan Topikal) : Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Schleroderma Renal Crisis*
155.	**PROMETHAZINE HCL** The following additional information shall be included on the label and in the package insert of liquid oral products containing Promethazine HCl: **WARNING** When used for treatment of cough and cold (a) "It (brand or generic names) should not be used in pediatric patients less than 2 years of age because of the potential for fatal respiratory depression". (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. **Reference:** ***Bil. (34) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*
156.	**PROPAFENONE** The following warning shall be included in the package insert of products containing propafenone: **Propafenone is not recommended for treatment of less severe arrhythmias such as nonsustained ventricular tachycardias or frequent premature ventricular contractions even if the patients are symptomatic, because of recent evidence in the US of increase mortality in patients with non-lifethreatening arrhythmias who were treated with encainide and flecainide.**

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157.	**PROPOFOL** The following statement shall be included in the package inserts of products containing Propofol: **a) WARNINGS AND PRECAUTIONS** Propofol is not recommended for paediatric general anaesthesia and sedation because its safety and effectiveness in these patients have not been established. There have been recent reports of adverse cardiac events and deaths associated with its use in paediatric intensive care. Although there is no evidence of a causal link of death with propofol in these cases, the drug could not be ruled out as a contributing factor. Until further data establishing its safety and delineating its appropriate dose range are available, propofol should not be used in paediatric intensive care. There have been very rare reports of epileptiform movement in epileptics and non-epileptics occurring during induction orbemergence from anaesthesia induced by propofol. **b) INTERACTIONS:** A need for lower propofol doses has been observed in patients taking valproate. When used concomitantly, a dose reduction of propofol may be considered. **c) ADVERSE EFFECTS/UNDESIRABLE EFFECTS:** Reproductive system and breast disorders: Frequency "not known": Priapism **References:** **Directive No. 7, 2018**. ***BPFK/PPP/07/25(7) Jld.2*** *Direktif Untuk Semua Produk Yang Mengandungi Propofol dan Sodium Valproate : Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Interaksi Ubat* **Directive No. 16, 2020**. ***NPRA.600-1/9/13(7)*** *Direktif Untuk Semua Produk Yang Mengandungi Propofol: Pengemaskinian Sisip Bungkusan Dengan Penambahan Maklumat Keselamatan Berkaitan Risiko Priapism*

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158.	**PROPOLIS (ORAL)** For products containing Propolis (for oral use), please state: - **"This product contains propolis and may cause severe allergic reactions including fatal anaphylactic reaction in susceptible individuals."** - **"Asthma and allergy sufferers may be at a greater risk."**
159.	**PROPOLIS (TOPICAL)** The following information shall be included on the labels and/ or package inserts of products containing Propolis (for topical use): **WARNINGS** Propolis may cause allergic skin reaction. **References:** ***Bil. (48) dlm. BPFK/02/5/1.3*** *Pernyataan Amaran Pada Label dan Sisip Bungkusan Produk Yang Mengandungi Propolis (Topikal) dan Royal Jelly (Semua Bentuk)* ***Bil. (56) dlm. BPFK/02/5/1.3*** *Pernyataan Amaran Pada Label dan Sisip Bungkusan Produk yang Mengandungi Propolis (topikal) dan Royal Jelly (Semua Bentuk)*

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160.	**PROPYLTHIOURACIL** The following statement shall be included in the package inserts of products containing propylthiouracil: **[1]WARNINGS AND PRECAUTIONS** Potential risk of serious hepatoxicity or liver injury including liver failure and death. Patients who are initiated with propylthiourasil should be closely monitored for signs and symptoms of liver injury (e.g. fatigue, weakness, vague abdominal pain, loss of appetite, itching, easy bruising or yellowing of the eyes or skin) especially during the first six months. If liver injury is suspected, promptly discontinue propylthiouracil therapy. Propylthiouracil should not be used in pediatric patients unless the patient is allergic to or intolerant of the alternatives available. [2]The following boxed warning shall be included in the package inserts of products containing propylthiouracil: ***BOXED WARNING*** *Severe liver injury and acute liver failure, in some cases fatal, have been reported in patients treated with propylthiouracil. These reports of hepatic reactions include cases requiring liver transplantation in adult and pediatric patients.* *Propylthiouracil should be reserved to patients who cannot tolerate carbimazole/ methimazole and in whom radioactive iodine therapy or surgery are not appropriate treatments for management of hyperthyroidism.* *Because of the risk of fetal abnormalities associated with carbimazole/ methimazole, propylthiouracil may be the treatment of choice when an antithyroid drug is indicated during or just prior to the first trimester of pregnancy (See Warnings and Precautions).* **References:** ***Circular [1]Bil (41) dlm. BPFK/PPP/01/03:*** *Kenyataan Amaran Berkaitan Dengan "Potential for an Increase in Risk of Hepatotoxicity" yang Perlu Dimuatkan Pada Sisip Bungkusan Produk Propylthiouracil* ***Circular [2]Bil (55) dlm. BPFK/PPP/01/03:*** *Kenyataan Amaran Berbentuk "Boxed Warning" Yang Wajib Dimuatkan Pada Sisip Bungkusan Produk Propylthiouracil Dengan "Severe Liver Injury"*

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161.	**PROTON PUMP INHIBITORS (PPI)** The following statements shall be included in the package insert and RiMUP of pharmaceutical products containing Proton Pump Inhitors (PPI): **Package Insert** **1. Warnings and Precautions:** Regular Surveillance Patients on proton pump inhibitor treatment (particularly those treated for long term) should be kept under regular surveillance. Subacute Cutaneous Lupus Erythematosus (SCLE) Proton pump inhibitors are associated with very infrequent cases of subacute cutaneous lupus erythematosus (SCLE). If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping {product name}. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors. Hypomagnesaemia Severe hypomagnesaemia has been reported in patients treated with PPI like {product name} for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who take PPI with digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment. Fracture Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10–40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Clostridium Difficile Diarrhea Published observational studies suggest that PPI therapy may be associated with an increased risk of Clostridium difficile associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Vitamin B12 Deficiency Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed. **2. Adverse Effects/ Undesirable Effects:** Gastrointestinal disorders Microscopic colitis: Frequency 'not known' Subacute Cutaneous Lupus Erythematosus (SCLE) Skin and subcutaneous tissue disorders Frequency 'not known': Subacute cutaneous lupus erythematosus Interstitial Nephritis Renal and urinary disorders: Interstitial nephritis Hypomagnesaemia Metabolism and nutritional disorders Frequency "not known": hypomagnesaemia. Fracture Musculoskeletal disorders Frequency "uncommon": Fracture of the hip, wrist or spine. Clostridium Difficile Diarrhea Infections & infestations: Clostridium difficile associated diarrhea. Fundic Gland Polyps (Benign) Gastrointestinal disorders Frequency "common": Fundic gland polyps (benign) Vitamin B12 Deficiency Metabolic/Nutritional: Vitamin B12 deficiency

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	3. Warnings and Precautions - Interference with laboratory tests Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. If the patient(s) are due to have a test on Chromogranin A level, [product name] treatment should be stopped for at least 5 days before CgA measurements to avoid this interference (see section Pharmacodynamic). If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment. **4. Pharmacodynamic** During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range. **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **i. Side Effects:** When you are taking this medicine, your doctor will want to monitor you (especially if you are taking it for long term). Hence, you should report any new and exceptional symptoms and circumstances whenever you see your doctor. Please tell your doctor promptly if you get any of the symptoms below: • Rash (especially in areas exposed to the sun), possibly with pain in the joints (Subacute Cutaneous Lupus Erythematosus, SCLE) • Fever, extreme tiredness, pus/blood in urine. • Involuntary muscle contractions, disorientation, convulsions, dizziness, increased heart rate • Fracture in the hip, wrist or spine. • Watery stool, stomach pain and fever that do not go away • Anemic (pale skin, weakness, tiredness or lightheadedness), shortness of breath, a smooth tongue, nerver problems (numbness or tingling, muscle weakness and problems walking), vision loss and mental problems (depression, memory loss or behavioral changes).

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	a) Subacute Cutaneous Lupus Erythematosus (SCLE) Frequency "not known" b) Interstitial Nephritis Kidney problems (interstitial nephritis) c) Hypomagnesaemia Frequency "not known": Low levels of magnesium can also lead to a reduction in potassium or calcium levels in the blood. d) Fracture Frequency "uncommon": Tell your doctor if you have osteoporosis or if you are taking corticosteroids (which can ncrease the risk of osteoporosis). e) Clostridium Difficile Diarrhea Severe diarrhoea which may be caused by an infection (Clostridium difficile) in your intestines. f) Fundic Gland Polyps (Benign) Frequency "Common": Benign polyps in the stomach g) Vitamin B12 Deficiency Proton pump inhibitors may cause vitamin B12 deficiency. h) Inflammation in the large bowel Frequency 'not known': Inflammation in the large bowel, that causes persistent watery diarrhea **ii. Before you start to use it** Tell your doctor before taking this medicine, if you are due to have a specific blood test (Chromogranin A). **References:** **Directive No. 16, 2017.** ***BPFK/PPP/07/25 (21) Jld. 1*** *Direktif Untuk Semua Produk Yang Mengandungi Proton Pump Inhibitors (PPI): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Risiko Kesan Advers Akibat Penggunaan Jangka Panjang (no. 1, 2, i)* **Directive No. 15, 2017.** ***BPFK/PPP/07/25 (20) Jld. 1*** *Direktif Untuk Semua Produk Yang Mengandungi Proton Pump Inhibitors (PPI): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Elevated Circulating Levels of Chromogranin A (CgA) (no. 3, 4, ii)* **Directive No. 7, 2020.** ***BPFK/PPP/07/25 (7) Jld. 4*** *Direktif Untuk Semua Produk Yang Mengandungi Proton Pump Inhibitors (PPI) Termasuk Produk Kombinasi: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Microscopic Colitis*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
162.	**PSEUDOEPHEDRINE** The following statement shall be included on the labels and in the package inserts of liquid oral products containing Pseudoephedrine: **WARNING** When used for treatment of cough and cold: (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. **Reference:** ***Bil. (34) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*
163.	**PSYCHOTROPIC PRODUCTS** The following statement shall be included conspicuously on the labels of all psychotropic products: **CAUTION:** This preparation may be habit forming on prolonged use.
164.	**PSYLLIUM/ PLANTAGO (SEED/ HUSK)** For products containing Psyllium/ Plantago (Seed/ Husk), please state: - **"If the constipation does not resolve within 3 days or if abdominal pain occurs or in case of any irregularity of faeces, the use of psyllium should be discontinued and medical advice must be sought."** **"Please consume a large amount of fluid/ water when taking this product."**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
165.	**RED YEAST RICE *(Monascus purpureus)*** "This product contains naturally occurring lovastatin. Please consult your doctor/ pharmacist before using this product." "Do not take this product if you are already on statin products (lovastatin, atorvastatin, fluvastatin, prasvastatin, simvastatin, rosuvastatin, etc). "If you experience any allergic reactions or side effects such as lethargy, body and muscle aches, please stop using this product" "Concurrent use of fibrates may cause severe myositis and myoglobinuria."
166.	**RETINOID (ORAL)** The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> of products containing retinoid (oral); **<u>Package Insert</u>** **a) Warnings and Precautions:** <u>Psychiatric symptoms</u> Depression, depression aggravated, anxiety, and mood alterations have been reported in patients treated with systemic retinoids. Particular care should be taken in patients with a history of depression. Patients should be monitored for signs of depression and referred for appropriate treatment if necessary. Awareness by family or friends may be useful to detect mental health deterioration. *An additional statement should also be included in the package insert of oral isotretinoin: Suicidal ideation, suicide attempts and suicide have been reported in patients treated with isotretinoin.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Consumer Medication Information Leaflet (RiMUP) **a) Before you use [product name]:** Talk to your doctor before taking [product name] If you have ever had any kind of mental health problems. This includes depression, aggressive tendencies or mood changes. *An additional statement should also be included in the RiMUP of oral isotretinoin: It also includes suicidal thoughts. Mental health problems Your mood may be affected while taking [product name]. You may not notice some changes in your mood and behaviour and so it is very important that you tell your friends and family that you are taking this medicine. They may notice these changes and help you quickly identify any problems that you need to talk to your doctor about. **Reference: Directive No. 6, 2019.** ***BPFK/PPP/07/25 (6) Jld. 3*** *Direktif Untuk Semua Produk Yang Mengandungi Retinoid (Oral): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Neuropsychiatric Disorders*
167.	**RETINOIDS (ORAL) INDICATED FOR TREATMENT OF SKIN DISEASES** The following statements shall be included in the label, package insert and Consumer Medication Information Leaflet (RiMUP) of products containing oral retinoids indicated for treatment of skin diseases: **Label** A boxed warning should be added to the outer packaging as follows: **WARNING** CAN SERIOUSLY HARM AN UNBORN BABY Women must use effective contraception Do not use if you are pregnant or you think you may be pregnant **Package Insert** **a) Contraindications:** • Pregnant women • Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met (See Section Warnings and Precautions)

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	b) Warnings and Precautions: **Teratogenic effects** [Product name] is a powerful human teratogen inducing a high frequency of severe and life threatening birth defects. **[Product name] is strictly contraindicated in:** - Pregnant women - Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met **Pregnancy Prevention Programme** [Product name] is contraindicated in women of childbearing potential unless all of the following conditions of the Pregnancy Prevention Programme are met: • [approved indications] (See Section Indications) • The potential for pregnancy must be assessed for all female patients. • She understands the teratogenic risk. • She understands the need for frequent follow-up (e.g. on a monthly basis). • She understands and accepts the need for effective contraception, without interruption, 1 month before starting treatment, throughout the entire duration of treatment and for 1 month* [*3 years for acitretin] after the end of treatment. At least one highly effective method of contraception (i.e. a user-independent form) or two complementary user-dependent forms of contraception should be used. • Individual circumstances should be evaluated in each case, when choosing the contraception method, involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures. • Even if she has amenorrhea she must follow all the advice on effective contraception. • She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy or if she might be pregnant. • She understands the need and accepts to undergo regular pregnancy testing before, ideally monthly during treatment and 1 month after stopping treatment [for acitretin this statement should be - She understands the need and accepts to undergo regular pregnancy testing before, ideally monthly during treatment and periodically with 1-3 monthly intervals for a period of 3 years after stopping treatment]. • She has acknowledged that she has understood the hazards and necessary precautions associated with the use of [product name]. These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	The prescriber must ensure that: • The patient complies with the conditions for pregnancy prevention as listed above, including confirmation that she has an adequate level of understanding. • The patient has acknowledged the aforementioned conditions. • The patient understands that she must consistently and correctly use one highly effective method of contraception (i.e. a user-independent form) or two complementary user-dependent forms of contraception, for at least 1 month prior to starting treatment and is continuing to use effective contraception throughout the treatment period and for at least 1 month* [*3 years for acitretin] after cessation of treatment. • Negative pregnancy test results have been obtained before, during and 1 month after the end of treatment. The dates and results of pregnancy tests should be documented. for acitretin this last bullet point should be] • Negative pregnancy test results have been obtained before, during and periodically with 1-3 monthly intervals for a period of 3 years after stopping treatment. The dates and results of pregnancy tests should be documented. If pregnancy occurs in a woman treated with [product name], treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice. If pregnancy occurs after stopping treatment there remains a risk of severe and serious malformation of the fetus. This risk persists until the product has been completely eliminated, which is within one month* following the end of treatment [*3 years for acitretin]. **Contraception** Female patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. If the prescribing physician is not in a position to provide such information the patient should be referred to the relevant healthcare professional. As a minimum requirement, female patients of childbearing potential must use at least one highly effective method of contraception (i.e. a user-independent form), or two complementary user-dependent forms of contraception. Contraception should be used for at least 1 month prior to starting treatment, throughout treatment and continue for at least 1 month* [*3 years for acitretin] after stopping treatment with [product name], even in patients with amenorrhea. Individual circumstances should be evaluated in each case, when choosing the contraception method involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Pregnancy testing Prior to starting therapy At least one month after the patient has started using contraception, and shortly (preferably a few days) prior to the first prescription, the patient should undergo a medically supervised pregnancy test. This test should ensure the patient is not pregnant when she starts treatment with [product name]. Follow-up visits Follow-up visits should be arranged at regular intervals, ideally monthly. Follow-up pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber. End of treatment 1 month after stopping treatment, women should undergo a final pregnancy test. [for acitretin this last paragraph should be] Women should undergo pregnancy test periodically with 1-3 monthly intervals for a period of 3 years after stopping treatment. **Prescribing and dispensing restrictions** For women of childbearing potential, the prescription duration of [product name] ideally be limited to 30 days in order to support regular follow up, including pregnancy testing and monitoring. Ideally, pregnancy testing, issuing a prescription and dispensing of [product name] should occur on the same day. This monthly follow-up will allow ensuring that regular pregnancy testing and monitoring is performed and that the patient is not pregnant before receiving the next cycle of medication. **Male patients** The available data suggest that the level of maternal exposure from the semen of the patients receiving [product name] is not of a sufficient magnitude to be associated with the teratogenic effects of [product name]. Male patients should be reminded that they must not share their medication with anyone, particularly not females. **Additional precautions** Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment. Patients should not donate blood during therapy and for 1 month* [*3 years for

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	acitretin] following discontinuation of [product name] because of the potential risk to the foetus of a pregnant transfusion recipient. **Educational material** In order to assist healthcare professionals and patients in avoiding fetal exposure to [product name] the Product Registration Holder will provide educational material to reinforce the warnings about the teratogenicity of [product name], to provide advice on contraception before therapy is started and to provide guidance on the need for pregnancy testing. Full patient information about the teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme should be given by the physician to all patients, both male and female. *Please also refer to* ***Appendix 22: Educational Materials*** **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [product name]:** **WARNING** CAN SERIOUSLY HARM AN UNBORN BABY Women must use effective contraception Do not use if you are pregnant or you think you may be pregnant When you must not use it: • If you are pregnant or breast-feeding • If there is any chance you could become pregnant **Women must use effective contraception before, during and after taking [product name]:** • You must agree to use at least one very reliable method of contraception (for example an intra uterine device or contraceptive implant) or, two effective methods that work in different ways (for example a hormonal contraceptive pill and a condom). Discuss with your doctor which methods would be suitable for you. • You must use contraception for a month before taking [product name], during treatment and for a month* afterwards [*for acitretin should be 3 years]. • You must use contraception even if you do not have periods or you are not sexually active (unless your doctor decides this is not necessary).

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Women must agree to pregnancy testing before, during and after taking [product name]: • You must agree to regular follow-up visits, ideally every month. • You must agree to have regular pregnancy tests, ideally every month during treatment and, because some medicine may still be left in your body, 1 month after stopping [product name] (unless your doctor decides this is not necessary in your case). {for acitretin: 'every 1 to 3 months for 3 years after stopping [product name]'}. • You must agree to extra pregnancy tests if your doctor asks you. • You must not get pregnant during treatment or for a month afterwards because some medicine may still be left in your body. for acitretin this last bullet point should be: • You must not get pregnant during treatment or for 3 years afterwards because some medicine may still be left in your body. If you get pregnant while taking [product name], stop taking the medicine straight away, and contact your doctor. Also, if you become pregnant within one month* [3* years for acitretin] after you stop taking [product name], you should contact your doctor. **Advice for men** The levels of oral retinoid in the semen of men taking [product name] are too low to harm their partners' unborn baby. However, you must never share your medication with anyone, especially females. **Additional precautions** You should never give this medicinal product to another person. Please take any unused capsules to your pharmacist at the end of treatment. You should not donate blood during treatment with this medicine and for 1 month* [*3 years for acitretin] after stopping [product name] because an unborn baby could be harmed if a pregnant patient receives your blood. **Reference: Directive No. 16, 2019.** ***BPFK/PPP/07/25 (16) JId.3*** *Direktif Untuk Semua Produk Yang Mengandungi Retinoid Yang Diindikasikan Untuk Rawatan Penyakit Kulit (Termasuk Topikal): Pengemaskinian Label, Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Bagi Memperkukuhkan Maklumat Keselamatan Berkaitan Kesan Teratogenik Serta Penyediaan Bahan-bahan Pengajaran (Educational Materials) Bagi Produk Yang Mengandungi Oral Retinoid Yang Diindikasikan Untuk Rawatan Penyakit Kulit*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
168.	**RETINOIDS (TOPICAL)** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of topical products containing retinoids: **Package Insert** **a) Contraindications:** • Pregnancy (see Section Pregnancy and Lactation) • Women planning a pregnancy **b) Pregnancy and Lactation [replacing specific labeling requirements – Tretinoin Topical]:** Orally administered retinoids have been associated with congenital abnormalities. When used in accordance with the prescribing information, topically administered retinoids are generally assumed to result into low systemic exposure due to minimal dermal absorption. However, there could be individual factors (e.g. damaged skin barrier, excessive use) that contribute to an increased systemic exposure. [Product name] is contraindicated (see Section Contraindications) in pregnancy, or in women planning a pregnancy. If the product is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued. **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [product name]:** Do not use [product name] if you are pregnant or thinking of becoming pregnant. Your doctor can give you more information. **Reference: Directive No. 16, 2019.** ***BPFK/PPP/07/25 (16) Jld.3*** *Direktif Untuk Semua Produk Yang Mengandungi Retinoid Yang Diindikasikan Untuk Rawatan Penyakit Kulit (Termasuk Topikal): Pengemaskinian Label, Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Bagi Memperkukuhkan Maklumat Keselamatan Berkaitan Kesan Teratogenik Serta Penyediaan Bahan-bahan Pengajaran (Educational Materials) Bagi Produk Yang Mengandungi Oral Retinoid Yang Diindikasikan Untuk Rawatan Penyakit Kulit*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
169.	**RISPERIDONE** The following statement shall be included in the package inserts of products containing Risperidone: **Warnings and Precautions** **Intraoperative Floppy Iris Syndrome** Intraoperative floppy iris syndrome (IFIS) has been observed during cataract surgery in patients treated with medicines with alpha1a-adrenergic antagonist effect, including risperidone. IFIS may increase the risk of eye complications during and after the operation. Current or past use of medicines with alpha1a-adrenergic antagonist effect should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping alpha1 blocking therapy prior to cataract surgery has not been established and must be weighed against the risk of stopping the antipsychotic therapy. **Adverse Effects / Undesirable Effects** **Postmarketing Data** Eye Disorders Frequency: Not known – Floppy iris syndrome (intraoperative) **Reference:** ***Bil. (17) dlm.BPFK/PPP/01/03 Jld.3*** *Pekeliling Untuk Mengemaskini Sisip Bungkusan Semua Produk Yang Mengandungi Risperidone Atau Paliperidone Dengan Amaran Berkaitan Risiko Intraoperative Floppy Iris Syndrome (IFIS) Pada Pesakit Yang Menjalani Pembedahan Katarak*
170.	**ROCURONIUM** The following statements shall be included in the package insert for products containing Rocuronium; **Package Insert** **a) Adverse Effects/ Undesirable Effects:** Cardiac disorders Frequency 'not known': Kounis Syndrome **Reference: Directive No. 11, 2021**. ***NPRA.600-1/9/13(21)*** *Direktif Untuk Semua Produk Yang Mengandungi Rocuronium: Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Risiko Kounis Syndrome*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
171.	**ROSIGLITAZONE** 1. The following **black box warning** shall be included in the first part of package inserts of products containing Rosiglitazone as single ingredient or in combination with other active ingredients: • Rosiglitazone is contraindicated in patients with established NYHA Class I to IV heart failure and in patients with known ischaemic heart disease, particularly in those taking nitrates. • Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients. Patients on rosiglitazone should be monitored carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of rosiglitazone must be considered. 2. The following information shall be included in the package inserts of products containing Rosiglitazone as single ingredient or in combination with other active ingredients: **CONTRAINDICATIONS** Rosiglitazone is contraindicated in patients with NYHA Class I to IV heart failure or history of cardiac failure, patients with known ischaemic heart disease and patients with Acute Coronary Syndrome (unstable angina, non-ST segment elevation myocardial infarction (NSTEMI) and ST segment elevation myocardial infarction. **WARNINGS AND PRECAUTIONS** Rosiglitazone has been shown to be associated with an increased risk of myocardial ischaemia (angina, infarction) in pooled short term clinical studies compared to combined active/placebo control (2.00% versus 1.53%). Death from myocardial ischaemic events occurred in 0.15% on rosiglitazone – containing regimens and 0.12% on comparator regimen. **Reference: Directive No. 10, 2010.** ***Bil. (6) dlm. BPFK/PPP/01/03 Jilid 1*** *Direktif Memperketatkan Penggunaan Rosiglitazone dan Memperkukuhkan Amaran Berkaitan Dengan Risiko Kesan Advers Kardiovaskular Pada Sisip Bungkusan Semua Produk Rosiglitazone Termasuk Produk Kombinasi*
172.	**ROSUVASTATIN** The following information shall be included on the labels and/or package inserts of products containing Rosuvastatin:

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	DOSAGE AND ADMINISTRATION Dosage in patients with pre-disposing factors to myopathy The recommended start dose is 5 mg in patients with pre-disposing factors to myopathy Concomitant Therapy Rosuvastatin is a substrate of various transporter proteins (e.g. OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when rosuvastatin is administered concomitantly with certain medicinal products that may increase the plasma concentration of rosuvastatin due to interactions with these transporter proteins (e.g. certain protease inhibitors including combinations of ritonavir with atazanavir, lopinavir, and/or tipranavir). Whenever possible, alternative medications should be considered, and if necessary, consider temporarily discontinuing [Product Name] therapy. In situations where co-administration of these medicinal products with rosuvastatin is unavoidable, the benefit and the risk of concurrent treatment and rosuvastatin dosing adjustments should be carefully considered. **CONTRAINDICATIONS** [Product Name] is contraindicated in patients receiving concomitant cyclosporine. **WARNINGS AND PRECAUTIONS** Skeletal Muscle Effects Gemfibrozil increases the risk of myopathy when given concomitantly with some HMG-CoA reductase inhibitors. Therefore, the combination of rosuvastatin and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of rosuvastatin with fibrates or niacin should be carefully weighed against the potential risks of such combinations. All generic products containing Rosuvastatin should update their package inserts respectively according to the innovator's information such as parts for Interactions, Pharmacokinetics and other parts deemed relevant. **Reference: Directive No. 9, 2014**. ***Bil. (16) dlm. BPFK/PPP/07/25*** *Direktif Untuk Semua Produk Rosuvastatin: Mengehadkan Dos Penggunaan Rosuvastatin Untuk Mengurangkan Risiko Kecederaan Otot*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
173.	**ROXITHROMYCIN** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing Roxithromycin; **Package Insert** **a) Warnings and Precautions:** In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCARs) [e.g. Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP)], [product name] should be discontinued immediately and appropriate treatment should be urgently initiated. **b) Adverse Effects/Undesirable Effects:** Skin and Subcutaneous Tissue Disorders Frequency not known: severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP). **Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects:** [Product name] may cause severe allergy and serious skin reactions. Stop using [Product name] and seek medical assistance immediately if you experience any of the following symptoms: • skin reddening, blisters, rash, fever, sore throat or eye irritation **Reference: Directive No. 22, 2018.** ***Bil. (22) dlm. BPFK/PPP/07/25 Jld.2*** *Direktif Untuk Semua Produk Yang Mengandungi Azithromycin, Clarithromycin, Erythromycin dan Roxithromycin: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Severe Cutaneous Adverse Reactions (SCARs)*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
174.	**ROYAL JELLY** The following information shall be included on the labels and/or package inserts of products containing Royal jelly: **WARNINGS** This product contains royal jelly and may cause severe allergic reactions including fatal anaphylactic reactions in susceptible individuals. Asthma and allergy sufferers may be at the greater risk. **References:** ***Bil. (48) dlm. BPFK/02/5/1.3*** *Pernyatan Amaran Pada Label dan Sisip Bungkusan Produk Yang Mengandungi Propolis (Topikal) dan Royal Jelly (Semua Bentuk)* ***Bil. (56) dlm. BPFK/02/5/1.3*** *Pernyataan Amaran pada Label dan Sisip Bungkusan Produk yang Mengandungi Propolis (Topikal) dan Royal Jelly (Semua Bentuk)* ***Bil. (12) dlm. BPFK/PPP/01/03*** *Pernyataan Amaran Pada Label dan Sisip Bungkusan Produk Yang Mengandungi Royal Jelly (Produk Kosmetik)*
175.	**SACCHAROMYCES BOULARDII** The following statements shall be included in the package insert, Consumer Medication Information Leaflet (RiMUP) and label of products containing *Saccharomyces boulardii*; **Package Insert** **a) Contraindications:** • Patients having a central venous catheter • Critically ill patients or immunocompromised patients due to a risk of fungaemia (See Section Warnings & Precautions) **b) Warnings and Precautions:** There have been very rare cases of fungaemia reported mostly in patients with central venous catheter, critically ill or immuno-compromised patients, most often resulting in pyrexia. In most cases, the outcome has been satisfactory after cessation of treatment by *Saccharomyces boulardii*, administration of antifungal treatment and removal of the catheter when necessary. However, the outcome was fatal in some critically ill patients (see Section Contraindications & Section Adverse Effects/Undesirable Effects).

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	c) Adverse Effects/Undesirable Effects: Infections and Infestations Very rare: Fungaemia in patients with a central venous catheter and in critically ill or immunocompromised patients (see Section Warnings and Precautions). **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [product name]:** When you must not take it Do not take this product if you are immunocompromised (altered/weakened immune system) or have central venous catheter. **b) Side Effects:** Very rare side effects: Penetration of yeast into blood (fungaemia) **Label** Please consult your doctor/pharmacist before using this product. Do not take this product if you are immunocompromised (altered/ weakened immune system) or have central venous catheter. **Reference: Directive No. 23, 2018.** ***Bil. (23) BPFK/PPP/07/25 Jld.2*** *Direktif Untuk Semua Produk Yang Mengandungi Saccharomyces Boulardii: Pengemaskinian Label, Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Fungaemia*
176.	**SALBUTAMOL** 1. The following information shall be included in the package inserts of products containing Salbutamol in **injection** dosage form: • As maternal pulmonary oedema and myocardial ischaemia have been reported during or following premature labour in patients receiving beta2 – agonists, careful attention should be given to fluid balance and cardio-respiratory function, including ECG monitoring. If signs of pulmonary oedema and myocardial ischaemia develop, discontinuation of treatment should be considered. • Due to the risk of pulmonary oedema and myocardial ischaemia that has been observed during the use of beta2-agonists in the treatment of premature labour, before these products are given to any patient with known heart disease, an adequate assessment of the patients's cardiovascular status should be made by

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	a physician experienced in cardiology. • Cautious use of salbutamol injections is required in pregnant patients when it is given for relief of bronchospasm so as to avoid interference with uterine contractibility. During IV infusion of salbutamol, the maternal pulse should be monitored and not normally allowed to exceed a steady rate of 140 beats per minute. 2. The following information shall be included in the package inserts and product literature of products containing Salbutamol in **oral tablet/ capsule** dosage form: • As maternal pulmonary oedema and myocardial ischaemia have been reported during or following premature labour in patients receiving beta2 – agonists, careful attention should be given to fluid balance and cardio-respiratory function, including ECG monitoring. If signs of pulmonary oedema and myocardial ischaemia develop, discontinuation of treatment should be considered. • Due to the risk of pulmonary oedema and myocardial ischaemia that has been observed during the use of beta2-agonists in the treatment of premature labour, before these products are given to any patient with known heart disease, an adequate assessment of the patients's cardiovascular status should be made by a physician experienced in cardiology. 3. The following warning statement shall be included in the package inserts of products containing Salbutamol in **injection and oral** dosage form under section of **Warning and Precautions**: **Tocolysis: Serious adverse reactions including death have been reported after administration of terbutaline/ salbutamol to women in labor. In the mother, these include increased heart rate, transient hyperglycaemia, hypokalaemia, cardiac arrhythmias, pulmonary oedema and myocardial ischaemia. Increased fetal heart rate and neonatal hypoglycaemia may occur as a result of maternal administration.** **References:** ***Bil. (6) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Mengenai Insiden* 'Myocardial Ischaemia' *Pada Wanita Mengandung Yang Menerima Rawatan* 'Beta Agonist' *Bagi Rawatan Melambatkan Kelahiran Pramatang Pada Sisip Bungkusan Kumpulan Produk Ini* **Directive No. 8, 2011.** ***Bil. (18) dlm. BPFK/PPP/01/03 Jld.1*** *Direktif Untuk Memperkukuhkan Amaran Berkaitan Dengan Risiko Kesan Advers Serius Pada Jantung Termasuk Kematian Dengan Penggunaan Produk Suntikan dan Oral Beta Agonis Dalam Rawatan Kelahiran Pra-Matang*
177.	**SALICYLIC ACID (NATURALLY OCCURING IN PLANTS E.G. WILLOW SALIX SPP)** Please state: "Individual allergic to aspirin/ other NSAID should avoid this product."

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178.	**SEDATIVE – HYPNOTIC PRODUCTS** The following statement shall be included in the package inserts of sedative-hypnotic products: **WARNINGS AND PRECAUTIONS** • Anaphylaxis (severe allergic reaction) and angioedema (severe facial swelling) which can occur as early as the first time the product is taken • Complex sleep – related behaviors which may include sleep driving, making phone calls, preparing and eating food while asleep **Reference:** ***Bil. (75) dlm. BPFK/02/5/1.3*** *Keputusan Mesyuarat PBKD - Pernyataan Amaran Pada Sisip Bungkusan Semua Produk Sedatif-Hipnotik Oral Berkaitan dengan Risiko Complex Sleep - Related Behaviors Which May Include Sleep Driving, Making Phone Calls, Preparing and Eating Food (While Asleep)*
179.	**SELENIUM SULPHIDE** The following statement shall be included on the labels of products containing Selenium sulphide: **WARNING** Do not use on broken skin or inflamed. Avoid contact with eyes. (***AMARAN:*** *Selenium sulphide tidak boleh digunakan pada kulit yang pecah dan radang. Elakkan daripada terkena mata.*)
180.	**SENNA (CASSIA SPP.) – fruit/ pod/ semen and leaf and Rhubarb/ Radix et Rhizoma Rhei/ Rheum Palmatum/ Rheum Officinalis – root part** The following statement shall be included on the labels of products containing senna (*cassia spp.) – fruit/ pod/ semen and leaf and Rhubarb/ Radix et Rhizoma Rhei/ Rheum Palmatum/ Rheum Officinalis – root part:* • Do not use when abdominal pain, nausea or vomiting is present. • Frequent or prolonged use of this preparation may result in dependence towards the product and 'imbalanced electrolytes'. • Please consult a health care practitioner for use beyond 7 days.

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181.	**SIMVASTATIN** The following statement shall be included in the package inserts of products containing Simvastatin: **1. Dosage and Administration** The 80mg dose is only recommended in patients at high risk for cardiovascular complications who have not achieved treatment goals on lower doses and when the benefits are expected to outweigh the potential risks. Concomitant Therapy In patients taking fibrates (other than gemfibrozil and fenofibrate) concomitantly with [Product Name], the dose of [Product Name] should not exceed 10mg/day. In patients taking amiodarone, verapamil or diltiazem concomitantly with [Product Name], the dose of [Product Name] should not exceed 20mg/day. In patients taking amlodipine or lipid-lowering dose of niacin (≥1g/day) concomitantly with [Product Name], the dose of [Product Name] should not exceed 40mg/day. **2. Contraindications** • Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone). • Concomitant administration of gemfibrozil, cyclosporine, or danazol. **3. Interactions** Contraindicated Drugs Potent inhibitors of CYP3A4: Concomitant use with medicines labeled as having a potent inhibitory effect on CYP3A4 at therapeutic doses (e.g.: itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir or nefazodone) is contraindicated. If treatment with potent CYP3A4 inhibitors is unavoidable, therapy with simvastatin should be suspended during the course of treatment. Gemfibrozil, cyclosporine or danazol: Concomitant use of these drugs with simvastatin is contraindicated. Other Drugs • Other fibrates: The dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with fibrates other than gemfibrozil or fenofibrate. When simvastatin and fenofibrate are given

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	concomitantly, there is no evidence that the risk of myopathy exceeds the sum of the individual risks of each agent. Caution should be used when prescribing fenofibrate with simvastatin, as either agent can cause myopathy when given alone. Addition of fibrates to simvastatin typically provides little additional reduction in LDL-C, but further reductions of TG and further increases in HDL-C may be obtained. Combinations of fibrates with simvastatin have been used without myopathy in small short-term clinical studies with careful monitoring. • Amiodarone: In a clinical trial, myopathy was reported in 6% of patients receiving simvastatin 80 mg and amiodarone. The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone. • Calcium channel blockers: - Verapamil or diltiazem: In a clinical trial, patients on diltiazem treated concomitantly with simvastatin 80 mg had an increased risk of myopathy. The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with verapamil or diltiazem. - Amlodipine: In a clinical trial, patients on amlodipine treated concomitantly with simvastatin 80 mg had a slightly increased risk of myopathy. The dose of simvastatin should not exceed 40 mg daily in patients receiving concomitant medication with amlodipine. - Niacin (≥1g/day): The dose of simvastatin should not exceed 40mg daily in patients receiving concomitant medication with niacin (nicotinic acid) ≥ 1g/day. Cases of myopathy/rhabdomyolysis have been observed with simvastatin co-administered with lipid-modifying doses (≥ 1 g/day) of niacin. **Reference:** ***Bil. (18) dlm.BPFK/PPP/01/03 Jld.3*** *Pekeliling Untuk Mengemaskini Sisip Bungkusan Semua Produk Yang Mengandungi Simvastatin Dengan Memuatkan Kontraindikasi dan Had Dos Yang Baru*
182.	**SODIUM GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS** The following statements shall be included in the Consumer Medication Information Leaflet (RiMUP) of products containing Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors: **Consumer Medication Information Leaflet (RiMUP)** 'Seek immediate medical attention when symptoms such as nausea, vomiting, decreased appetite, abdominal pain, excessive thirst, difficulty in breathing, confusion, unusual fatigue or sleepiness, frequent urination and fruity-smelling breath occur'.

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183.	**SODIUM METABISULPHITE (EXCIPIENT)** The following statement shall be included in the package inserts of products containing Sodium metabisulphite: **WARNINGS AND PRECAUTIONS** This preparation contains Sodium metabisulphite that may cause serious allergic type reactions in certain susceptible patients. Do not use if known to be hypersensitive to bisulphites.
184.	**SODIUM VALPROATE** The following statements shall be included in the label, package insert and Consumer Medication Information Leaflet (RiMUP) of products containing sodium valproate: **Label** *A boxed warning should be added to the outer packaging as follows:* ***WARNING FOR WOMEN AND GIRLS*** *This medicine can seriously harm an unborn baby* *Always use effective contraception during treatment with sodium valproate* *If you are thinking about becoming pregnant, or if you are pregnant, contact your doctor urgently.* *You must CONTINUE taking sodium valproate unless your doctor tells you to stop* **Package Insert** **PANCREATITIS:** CASES OF LIFE-THREATENING PANCREATITIS HAVE BEEN REPORTED IN BOTH CHILDREN AND ADULTS RECEIVING VALPROATE. SOME OF THE CASES HAVE BEEN DESCRIBED AS HEMORRHAGIC WITH A RAPID PROGRESSION FROM INITIAL SYMPTOMS TO DEATH. CASES HAVE BEEN REPORTED SHORTLY AFTER INITIAL USE AS WELL AS AFTER SEVERAL YEARS OF USE. PATIENTS AND GUARDIANS SHOULD BE WARNED THAT ABDOMINAL PAIN, NAUSEA, VOMITING, AND/OR ANOREXIA CAN BE SYMPTOMS OF PANCREATITIS THAT REQUIRE PROMPT MEDICAL EVALUATION. IF PANCREATITIS IS DIAGNOSED, VALPROATE SHOULD BE DISCONTINUED.

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	a) Posology and Method of administration: Female children and women of childbearing potential Sodium valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated (see Contraindications, Warnings and precautions and Fertility, pregnancy and lactation sections). The benefit and risk should be carefully reconsidered at regular treatment reviews. Sodium valproate should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose should be divided into at least two single doses. **b) Contraindications:** Sodium valproate is contraindicated in the following situations: • In epilepsy - sodium valproate is contraindicated in pregnancy unless there is no suitable alternative treatment - sodium valproate is contraindicated in women of childbearing potential, unless the conditions of Pregnancy Prevention Programme are fulfilled (see Warnings and precautions and Fertility, pregnancy and lactation sections) • In bipolar disorder - sodium valproate is contraindicated in pregnancy - sodium valproate is contraindicated in women of childbearing potential, unless the conditions of Pregnancy Prevention Programme are fulfilled (see Female children, Women of childbearing potential, pregnant women section) **c) Warnings and Precautions:** **Female children, Women of childbearing potential, and pregnant women:** Sodium valproate has a high teratogenic potential and children exposed in utero to sodium valproate have a high risk for congenital malformations and neurodevelopmental disorders. Sodium valproate is contraindicated in the following situations: • In pregnancy unless there is no suitable alternative treatment for epilepsy indication. • In pregnancy for bipolar disorder indication. • In women of childbearing potential unless below conditions are fulfilled. <u>Conditions of Pregnancy Prevention Programme:</u> The prescriber must ensure that: • Individual circumstances should be evaluated in each case. Involving the patient in the discussion to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the

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		measures needed to minimise the risks. • The potential for pregnancy is assessed for all female patients. • The patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to sodium valproate in utero. • The patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed. In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible (see Fertility, Pregnancy and Lactation). Sodium valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with sodium valproate for the patient by a physician experienced in the management of epilepsy. • The patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception (for further details please refer to subsection contraception of this boxed warning), without interruption during the entire duration of treatment with sodium valproate. • The patient understands the need for regular (at least annual) review of treatment by a prescriber experienced in the management of epilepsy. • The patient understands the need to consult her physician as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception and before contraception is discontinued. • The patient understands the need to urgently consult her physician in case of pregnancy. • The patient has received the Patient Guide. • The patient has acknowledged that she has understood the hazards and necessary precautions associated with sodium valproate use (Annual Risk Acknowledgement Form). These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy. <u>Female children</u> The prescriber must ensure that: • The parents/caregivers of female children understand the need to contact the doctor once the female child using sodium valproate	

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		experiences menarche. • The parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to sodium valproate in utero. In patients who have experienced menarche, the prescriber must annually reassess the need for sodium valproate therapy and consider alternative treatment options. If sodium valproate is the only suitable treatment, the need for using effective contraception and all other conditions of the pregnancy prevention programme should be discussed. Every effort should be made by the prescriber to switch female children to alternative treatment before they reach adulthood. <u>Pregnancy test</u> Pregnancy must be excluded before start of treatment with sodium valproate. Treatment with sodium valproate must not be initiated in women of childbearing potential without a negative pregnancy test (plasma pregnancy test) result, confirmed by a healthcare provider, to rule out unintended use in pregnancy. <u>Contraception</u> Women of childbearing potential who are prescribed sodium valproate must use effective contraception without interruption during the entire duration of treatment with sodium valproate. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user independent form such as an intra-uterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case when choosing the contraception method, involving the patient in the discussion to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhea she must follow all the advice on effective contraception. <u>Annual treatment reviews by the prescriber</u> The prescriber should review at least annually whether sodium valproate is the most suitable treatment for the patient. The prescriber should discuss the Annual Risk Acknowledgement Form at initiation and during each annual review and ensure that the patient has understood its content. <u>Pregnancy planning</u> If a woman is planning to become pregnant, a prescriber experienced in the management of epilepsy must reassess sodium valproate therapy and consider alternative treatment options. Every effort should be made to switch to	

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appropriate alternative treatment prior to conception and before contraception is discontinued. If switching is not possible, the woman should receive further counselling regarding the risks of sodium valproate for the unborn child to support her informed decision-making regarding family planning.

In case of pregnancy

If a woman using sodium valproate becomes pregnant, she must be immediately referred to a doctor to re-evaluate treatment with sodium valproate and consider alternative treatment options. The patients with sodium valproate-exposed pregnancy and their partners should be referred to a doctor experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy.

Pharmacists must ensure that:

- The Patient Card is provided with every sodium valproate dispensation and that patients understand its content.
- Patients are advised not to stop sodium valproate medication and to immediately contact the prescriber in case of planned or suspected pregnancy.

Educational materials

In order to assist healthcare professionals and patients in avoiding exposure to sodium valproate during pregnancy, the Marketing Authorisation Holder has provided educational materials to reinforce the warnings, provide guidance regarding use of sodium valproate in women of childbearing potential and provide details of the Pregnancy Prevention Programme. A Patient Guide and Patient Card should be provided to all women of childbearing potential using sodium valproate.

An Annual Risk Acknowledgement Form needs to be used at time of treatment initiation and during each annual review of sodium valproate treatment by the prescriber. at treatment initiation, at the annual visit, and when a woman plans a pregnancy or is pregnant

Sodium valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with sodium valproate for the patient by a doctor experienced in the management of epilepsy.

*Please also refer to **Appendix 22: Educational Materials***

d) Fertility, Pregnancy and Lactation:

- Sodium valproate is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy.
- Sodium valproate is contraindicated as treatment for bipolar disorder during

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	pregnancy. • Sodium valproate is contraindicated for use in women of childbearing potential unless the above mentioned conditions of Pregnancy Prevention Programme are fulfilled (see Contraindications and Warnings and precautions sections) **Pregnancy Exposure Risk related to sodium valproate** Both sodium valproate monotherapy and sodium valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that antiepileptic polytherapy including sodium valproate is associated with a greater risk of congenital malformations than sodium valproate monotherapy. **<u>Teratogenicity and developmental effects</u>** **Congenital malformations** Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to sodium valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 -13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2-3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established. Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems. **Developmental disorders** Data have shown that exposure to sodium valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded. Studies in preschool children exposed in utero to sodium valproate show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems. Intelligence quotient (IQ) measured in school aged children (age 6) with a history of sodium valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to sodium valproate that the risk of intellectual impairment may be independent from maternal IQ. There are limited data on the long term outcomes.

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	Available data show that children exposed to sodium valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population. Limited data suggests that children exposed to sodium valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD). Female children and woman of childbearing potential (see **Contraindications and Warnings and precautions sections**) **If a Woman plans a Pregnancy** If a woman is planning to become pregnant, a doctor experienced in the management of epilepsy must reassess sodium valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception and before contraception is discontinued. If switching is not possible, the woman should receive further counselling regarding the risks of sodium valproate for the unborn child to support her informed decision-making regarding family planning. **Pregnant women** Sodium valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment. If a woman using sodium valproate becomes pregnant, she must be immediately referred to a doctor to consider alternative treatment options. During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for the mother and the unborn child. If in exceptional circumstances, despite the known risks of sodium valproate in pregnancy and after careful consideration of alternative treatment, a pregnant woman must receive sodium valproate for epilepsy. It is recommended to: - Use the lowest effective dose and divide the daily dose sodium valproate into several small doses to be taken throughout the day. - The use of a prolonged release formulation may be preferable to other treatment formulations to avoid high peak plasma concentrations. All patients with sodium valproate-exposed pregnancy and their partners should be referred to a doctor experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy. Specialised prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations. Folate supplementation before the pregnancy may decrease the risk of neural tube defects which may occur in all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations

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	due to sodium valproate exposure. **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [product name]:** ***WARNING FOR WOMEN AND GIRLS*** *This medicine can seriously harm an unborn baby* *Always use effective contraception during treatment with sodium valproate* *If you are thinking about becoming pregnant, or if you are pregnant, contact your doctor urgently.* *You must CONTINUE taking sodium valproate unless your doctor tells you to stop* Before you start to use it: - Tell your healthcare professionals if you are pregnant. - If you are a woman able to have a baby you must not take sodium valproate unless you use an effective method of birth control (contraception) at all times during your treatment with sodium valproate. **b) While you are using it:** Things you must do: - Schedule an urgent appointment with your doctor if you want to become pregnant or if you think you are pregnant. - If you are a parent or a caregiver of a female child treated with sodium valproate, you should contact their doctor once your child experiences their first period (menarche). Things you must not do: - Continue taking sodium valproate or using your birth control (contraception) until you have discussed your pregnancy or your plan to get pregnant with your doctor. Things to be careful of: - Sodium valproate can seriously harm an unborn baby when taken during pregnancy.

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	- The higher the dose, the higher the risks but all doses carry a risk. - It can cause serious birth defects and can affect the way in which the child develops as it grows. Birth defects which have been reported include spina bifida (where the bones of the spine are not properly developed); facial and skull malformations; heart, kidney, urinary tract and sexual organ malformations; limb defects. - If you take sodium valproate during pregnancy you have a higher risk than other women of having a child with birth defects that require medical treatment. Because sodium valproate has been used for many years it is known that in women who take sodium valproate around 10 babies in every 100 will have birth defects. This compares to 2-3 babies in every 100 born to women who don't have epilepsy. - It is estimated that up to 30-40% of preschool children whose mothers took sodium valproate during pregnancy may have problems with early childhood development. Children affected can be slow to walk and talk, intellectually less able than other children, and have difficulty with language and memory. - Autistic spectrum disorders are more often diagnosed in children exposed to sodium valproate and there is some evidence children may be more likely to develop symptoms of Attention Deficit Hyperactivity Disorder (ADHD). **c) Taking other medicines:** Some medicines and sodium valproate may interfere with each other, these include propofol (a medicine used before and during general anaesthesia). Tell your doctor that you are taking [product name] if you are going for an operation. **References:** **Directive No. 17, 2016.** ***BPFK/PPP/07/25 (3) Jld.1*** *Direktif Bagi Semua Produk Yang Mengandungi Sodium Valproate Bagi Memperkukuhkan Amaran Berkaitan Risiko Abnormal Pregnancy Outcomes* **Directive No. 7, 2018.** ***BPFK/PPP/07/25 (7) Jld.2*** *Direktif Untuk Semua Produk Yang Mengandungi Propofol dan Sodium Valproate: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Interaksi Ubat* **Directive No. 21, 2019.** ***BPFK/PPP/07/25 (21) Jld. 3*** *Direktif Untuk Semua Produk Yang Mengandungi Sodium Valproate: Pengukuhan Maklumat Keselamatan Pada Label, Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Berkaitan Risiko Kecacatan Kongenital dan Masalah Perkembangan Dalam Kalangan Bayi dan Kanak-Kanak Yang Terdedah Kepada Penggunaan Sodium Valproate Semasa Dalam Kandungan Serta Penyediaan Bahan-bahan Pengajaran (Educational Materials) Bagi Produk Yang Mengandungi Sodium Valproate*

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185.	**ST. JOHN'S WORT *(Hypericum perforatum)*** The following boxed statement shall be included on the labels of products containing St. John's Wort: Please consult your physician/ pharmacist before using this product if you are on any prescription medicines as there is possibility that interactions may occur with certain drugs. *(Sila dapatkan nasihat doktor/ ahli farmasi sebelum menggunakan produk ini, kerana kemungkinan berlakunya interaksi dengan penggunaan ubat preskripsi).*
186.	**STATINS** The following statement shall be included in the package inserts and RiMUP of ALL products containing statins (single active or in combination): **Package Insert** **a) INTERACTION**: Concurrent use of fibrates may cause severe myositis and myoglobinuria. **b) ADVERSE EFFECTS / UNDESIRABLE EFFECTS**: There have been rare post-marketing reports of cognitive impairment (e.g. memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally non-serious and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median 3 weeks). Increases in HbA1c and fasting blood glucose have been reported with statins. The risk of hyperglycemia, however, is outweighed by the reduction in vascular risk with statins. Musculoskeletal disorders: Frequency not known: Immune-mediated necrotizing myopathy **c) Warnings and Precautions:** There have been very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterized by: • persistent proximal muscle weakness and elevated serum creatine

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	kinase, which persist despite discontinuation of statin treatment; • muscle biopsy showing necrotizing myopathy without significant inflammation; • improvement with immunosuppressive agents. **Consumer Medication Information Leaflet (RiMUP)** **Side Effects** *If you have muscle problems that do not go away even after your doctor has told you to stop taking {product name}, please refer to your doctor. Your doctor may do further tests to diagnose the cause of your muscle problems.* **References:** **Directive No. 7, 2014.** ***Bil. (14) dlm.BPFK/PPP/07/25*** *Direktif Untuk Semua Produk Statin: Memperkukuhkan Amaran Berkaitan Risiko Kesan Advers Kognitif dan Peningkatan HBA1C Serta Fasting Blood Glucose (FBG)* **Directive No. 29, 2017.** ***BPFK/PPP/07/25 (34) Jld.1*** *Direktif Untuk Semua Produk Yang Mengandungi Statin: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Immune-Mediated Necrotizing Myopathy (IMNM)*
187.	**STRONTIUM RANELATE** 1. The following **black boxed warning** shall be included in the first part of package inserts of products containing Strontium Ranelate: *[Brand Name]* should only be used for whom treatment with other medicinal products approved for the treatment of osteoporosis is not possible due to, for example, contraindications or intolerance. *[Brand Name]* is contraindicated in patients with: • established, current or past history of ischaemic heart disease; peripheral arterial disease and/or cerebrovascular disease; • uncontrolled hypertension; • current or previous venous thromboembolic events (VTE); • temporary or permanent immobilisation. 2. The following statement shall be included in the package inserts of products containing Strontium Ranelate: **Indications** • Treatment of severe/established osteoporosis in postmenopausal women at high risk of fracture to reduce the risk of vertebral and hip fractures • Treatment of severe/established osteoporosis in men at increased risk of fracture

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	[Brand Name] should only be used for whom treatment with other medicinal products approved for the treatment of osteoporosis is not possible due to, for example, contraindications or intolerance. **Contraindications** • Established, current or past history of ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease • Uncontrolled hypertension **Warnings and precautions** **Cardiac ischaemic events** In pooled randomised placebo-controlled studies of post-menopausal osteoporotic patients, a significant increase in myocardial infarction has been observed in strontium ranelate treated patients compared to placebo. Before starting treatment, patients should be evaluated with respect to cardiovascular risk. Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with strontium ranelate after careful consideration. During [BRAND NAME] treatment, these cardiovascular risks should be monitored on a regular basis generally every 6 to 12 months. Treatment should be stopped if the patient develops ischaemic heart disease, peripheral arterial disease, cerebrovascular disease or if hypertension is uncontrolled. **Adverse Effects/ Undesirable Effects:** SOC Cardiac disorders: - Common: Myocardial infarction **Myocardial infarction** In pooled randomised placebo-controlled studies of post-menopausal osteoporotic patients, a significant increase of myocardial infarction has been observed in strontium ranelate treated patients as compared to placebo (1.7% versus 1.1%), with a relative risk of 1.6 (95% CI = [1.07; 2.38]). **Reference:** *Bil. (16) dlm.BPFK/PPP/01/03 Jld.3 Pekeliling Tentang Langkah-langkah Pengurangan Risiko Bagi Produk Yang Mengandungi Strontium Ranelate Susulan Risiko Kesan Advers Kardiovaskular*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
188.	**SUCCINYLATED GELATIN (MODIFIED FLUID GELATIN)** The following statements shall be included in the package insert of products containing Succinylated Gelatin (Modified Fluid Gelatin); **Warnings and Precautions:** Due to possible cross-reactions involving the allergen galactose-alpha-1,3-galactose (alpha-Gal), the risk of sensitization and consequent anaphylactic reaction to gelatin-containing solutions could be highly increased in patients with history of allergy to red meat (mammal meat) and offal and/or tested positive for anti-alpha-Gal IgE antibodies. In these patients, [Product name] should be administered only after a careful assessment of benefit/risk, including alternative treatments, and only under close supervision of well trained personnel with resuscitation equipment ready. **Reference: Directive No. 28, 2018.** ***BPFK/PPP/07/25 (28) Jld.2*** *Direktif Untuk Semua Produk Yang Mengandungi Succinylated Gelatin (Modified Fluid Gelatin): Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Risiko Cross-Reaction Yang Melibatkan Alergen Galactose-Alpha-1,3-Galactose (Alpha-Gal)*
189.	**SULFASALAZINE** The following statements shall be included in the Package Insert and Consumer Medication Information Leaflet (RiMUP) of products containing sulfasalazine: **Package Insert** **a) Warnings and Precautions:** Sulfasalazine or its metabolites may interfere with ultraviolet absorbance, particularly at 340 nm, and may cause interference with some laboratory assays that use nicotinamide adenine dinucleotide [NAD(H)] or nicotinamide adenine dinucleotide phosphate [NADP(H)]. Caution should be exercised in the interpretation of these laboratory results in patients who are receiving sulfasalazine (see Section Interactions). **b) Interactions:** Sulfasalazine or its metabolites may interfere with ultraviolet absorbance, particularly at 340 nm, and may cause interference with some laboratory assays that use NAD(H) or NADP(H) to measure ultraviolet absorbance around that wavelength. Examples of such assays may include alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase-muscle/brain (CK-MB), glutamate dehydrogenase (GLDH), ammonia, thyroxine, or glucose. Consult with the testing laboratory regarding the methodology used.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Caution should be exercised in the interpretation of these laboratory results in patients who are receiving sulfasalazine. Results should be interpreted in conjunction with clinical findings (see Section Warnings and Precautions). **c) Adverse Effects/Undesirable Effects:** Renal and urinary disorders Frequency 'not known' : Nephrolithiasis* * Adverse effects identified post-marketing. **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [Product Name]:** Before you start to use it Tell your doctor if you are taking or have recently taken [product name], or any other sulfasalazine containing products, because they may affect results of blood and urine tests. **b) Side effects:** - kidney stones and associated pain **References:** **Directive No. 20, 2019.** ***BPFK/PPP/07/25 (20) Jld. 3*** *Direktif Untuk Semua Produk Yang Mengandungi Sulfasalazine: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Gangguan Terhadap Ujian Makmal Yang Menggunakan Reaksi Dihydronicotinamide-Adenine Dinucleotide/ Dihydronicotinamide-Adenine Dinucleotide Phosphate (NADH/NADPH)* **Directive No. 1, 2021.** ***NPRA.600-1/9/13 (11)*** *Direktif Untuk Semua Produk Yang Mengandungi Mesalazine dan Sulfasalazine: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Nephrolithiasis*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
190.	**SULPHONAMIDES/ TRIMETHOPRIM** 1. The following statement shall be included on the labels of products containing Sulphonamides and Trimethoprim as single ingredient or in combination of both ingredients: Discontinue treatment with this drug immediately if skin rash or any sign of adverse reaction occurs. 2. The following statement shall be included in the package inserts of products containing Sulphonamides and Trimethoprim as single ingredient or in combination of both ingredients: Fatalities associated with the administration of sulphonamides and trimethoprim, either alone or in combination, have occurred due to severe reactions, including Steven-Johnson syndrome, toxic epidermal necrolysis and other reactions. The drug should be discontinued at the first appearance of skin rash or any sign of adverse reaction.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
191.	**SYNTHETIC SALMON CALCITONIN** 1. Indication and duration of use for products containing synthetic salmon calcitonin (according to the stated dosage forms) are restricted as follows, and the package insert of the product shall be amended accordingly: a) For dosage form: Injection *Prevention of acute bone loss due to sudden immobilisation such as in patients with recent osteoporotic fractures.* ***The duration of treatment should not be more than 4 weeks.*** *For the treatment of Paget's disease, only in patients who do not respond to alternative treatments or for whom such treatments are not suitable, for example those with severe renal impairment.* ***The duration of treatment is limited to 3 months.*** *Treatment of hypercalcaemia of malignancy.* b) For dosage form: Nasal spray *<u>Prevention of osteoporosis</u>: In acute bone loss due to sudden immobilisation such as in patients with recent osteoporotic fractures. Miacalcic should be supplemented with adequate doses of calcium and Vit D, as needed by the individual patient, to prevent further bone loss.* ***The maximum duration of treatment is 3 months.*** *<u>Paget's disease</u>, only in patients who do not respond to alternative treatments or for whom such treatments are not suitable.* ***The duration of treatment is normally 3 months.*** *<u>Algodystrophy or Sudeck's Disease (Neurodystrophic disorders)</u> due to various causes and predisposing factors such as posttraumatic painful osteoporosis, reflex dystrophy, shoulder arm syndrome, causalgia and drug-induced neurotrophic disorders.* ***The duration of treatment is up to 6 weeks.*** 2. Under "Dosage" in the package insert of products containing synthetic salmon calcitonin (injection and nasal spray), the following statement shall be stated: *The treatment duration in all indications should be limited to the shortest period of time possible and using the lowest effective dose.* **Reference: Directive No. 4, 2014.** ***Bil. (10) dlm.BPFK/PPP/07/25*** *Direktif Untuk Mengehadkan Indikasi dan Tempoh Penggunaan Produk Yang Mengandungi Calcitonin Salmon Sintetik Dalam Bentuk Injeksi dan Intranasal 'Nasal Spray' Berikutan Risiko Kanser*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
192.	**TABEBUIA SPP. (PAU D'ARCO)** The following warning statement shall be included on the labels of products containing Tabebuia spp. (Pau d'arco): "As the use of Tabebuia spp. (Pau d'arco) may increase the tendency of bleeding, please consult your physician/ pharmacist if you are on or intend to start using any other medicine and before you undergo any surgical/ dental procedure." (Memandangkan pengambilan Tabebuia spp. (Pau d'arco) boleh meningkatkan kemungkinan pendarahan, sila rujuk kepada doktor/ ahli farmasi sekiranya anda sedang atau akan menggunakan ubat lain dan sebelum prosedur pembedahan/ dental dijalankan)
193.	**TEMOZOLOMIDE** The following statement shall be included in the package inserts of products containing Temozolomide: **WARNINGS AND PRECAUTIONS** Hepatic injury, including fatal hepatic failure has been reported in patients receiving temozolomide. Baseline liver function tests should be performed prior to treatment initiation. If abnormal, physicians should assess the benefit/ risks prior to initiating temozolomide including the potential for fatal hepatic failure. For patients on a 42 days treatment cycle, liver function test should be repeated midway during this cycle. For all patients, liver function test should be checked after treatment cycle. For patient with significant liver function abnormalities, physicians should assess the benefit/ risks of continuing treatment. Liver toxicity may occur several weeks or more after the last reatment of temozolomide. **Reference: Directive No. 11, 2014.** ***Bil. (18) dlm. BPFK/PPP/07/25*** *Direktif Untuk Semua Produk Yang Mengandungi Temozolomide: Maklumat Keselamatan Baru Berkaitan Dengan Risiko Kecederaan Hati*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
194.	**TERBUTALINE** 1. The following statement shall be included in the package inserts of products containing Terbutaline in **injection** dosage form: • As maternal pulmonary oedema and myocardial ischaemia have been reported during or following premature labour in patients receiving beta2 – agonists, careful attention should be given to fluid balance and cardio-respiratory function, including ECG monitoring. If signs of pulmonary oedema and myocardial ischaemia develop, discontinuation of treatment should be considered. • Due to the risk of pulmonary oedema and myocardial ischaemia that has been observed during the use of beta2-agonists in the treatment of premature labour, before these products are given to any patient with known heart disease, an adequate assessment of the patients's cardiovascular status should be made by a physician experienced in cardiology. • Cautious use of terbutaline injections is required in pregnant patients when it is given for relief of bronchospasm so as to avoid interference with uterine contractibility. During IV infusion of terbutaline, the maternal pulse should be monitored and not normally allowed to exceed a steady rate of 140 beats per minute. 2. The following information shall be included in the package insert and product literature of products containing Terbutaline in **oral tablet/ capsule** dosage form: • As maternal pulmonary oedema and myocardial ischaemia have been reported during or following premature labour in patients receiving beta2 – agonists, careful attention should be given to fluid balance and cardio-respiratory function, including ECG monitoring. If signs of pulmonary oedema and myocardial ischaemia develop, discontinuation of treatment should be considered. • Due to the risk of pulmonary oedema and myocardial ischaemia that has been observed during the use of beta2-agonists in the treatment of premature labour, before these products are given to any patient with known heart disease, an adequate assessment of the patients's cardiovascular status should be made by a physician experienced in cardiology.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	3. The following warning statement shall be included in the package inserts of products containing terbutaline in **injection and oral** dosage form under section of **Warning and Precautions**: • **Tocolysis: Serious adverse reactions including death have been reported after administration of terbutaline/ salbutamol to women in labor. In the mother, these include increased heart rate, transient hyperglycaemia, hypokalaemia, cardiac arrhythmias, pulmonary oedema and myocardial ischaemia. Increased fetal heart rate and neonatal hypoglycaemia may occur as a result of maternal administration.** **References:** ***Bil. (6) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Mengenai Insiden* 'Myocardial Ischaemia' *pada Wanita Mengandung yang Menerima Rawatan* 'Beta Agonist' *Bagi Rawatan Melambatkan Kelahiran Pramatang Pada Sisip Bungkusan Kumpulan Produk Ini* **Directive No. 8, 2011.** ***Bil. (18) dlm. BPFK/PPP/01/03 Jilid 1*** *Direktif Untuk Memperkukuhkan Amaran Berkaitan Dengan Risiko Kesan Advers Serius Pada Jantung Termasuk Kematian Dengan Penggunaan Produk Suntikan dan Oral Beta Agonis dalam Rawatan Kelahiran Pra-Matang*
195.	**TESTOSTERONE** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing Testosterone; **Package Insert** **a) Warnings and Precautions:** Drug Abuse and Dependence Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indication and in combination with other anabolic androgenic steroids (AAS). Abuse of testosterone and other AAS are seen in adults and adolescents, including athletes and body builders. Testosterone and AAS abuse can lead to serious adverse outcomes particularly cardiovascular and psychiatric adverse events (See Section Adverse Effects/Undesirable Effects). If testosterone abuse is suspected, check serum testosterone concentrations to ensure they are within therapeutic range. However, testosterone levels may be in the normal or subnormal range in men abusing synthetic testosterone derivatives. Counsel patients concerning the serious adverse reactions associated with abuse of testosterone and AAS. Conversely, consider the possibility of testosterone and AAS abuse in suspected patients who present with serious cardiovascular or psychiatric adverse events.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Continued abuse of testosterone and other AAS may result in dependence and withdrawal symptoms. Individuals taking supratherapeutic doses of testosterone may experience withdrawal symptoms lasting for weeks or months which include depressed mood, major depression, fatigue, craving, restlessness, irritability, anorexia, insomnia, decreased libido and hypogonadotropic hypogonadism. Drug dependence in individuals using approved doses of testosterone for approved indications has not been documented. **b) Overdose:** Chronic Overdose Caused by Abuse Chronic overdose caused by abuse of testosterone and other anabolic androgenic steroids (AAS) can lead to serious adverse outcomes particularly cardiovascular and psychiatric adverse events (See Sections Warnings and Precautions and Adverse Effects/ Undesirable Effects). **c) Adverse Effects/Undesirable Effects:** Abuse-Related Adverse Reactions Serious adverse reactions have been reported in individuals who abuse testosterone and anabolic androgenic steroids (AAS) and include cardiac arrest, myocardial infarction, hypertrophic cardiomyopathy, congestive heart failure, cerebrovascular accident, hepatotoxicity, and serious psychiatric manifestations, including major depression, mania, paranoia, psychosis, delusions, hallucinations, hostility and aggression. The following adverse reactions have also been reported in men: transient ischemic attacks, convulsions, hypomania, irritability, dyslipidaemias, testicular atrophy, subfertility, and infertility. The following additional adverse reactions have been reported in women: hirsutism, virilisation, deepening of voice, clitoral enlargement, breast atrophy, male-pattern baldness, and menstrual irregularities. The following adverse reactions have been reported in male and female adolescents: premature closure of bony epiphyses with termination of growth, and precocious puberty. Because these reactions are reported voluntarily from a population of uncertain size and may include abuse of other agents, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Consumer Medication Information Leaflet (RiMUP) **a) How to use [product name]:** If you use too much (overdose): If you have taken more than the recommended dose of [product name], contact your doctor immediately or go to the Emergency Department of your nearest hospital. Do this even if there are no signs of discomfort or poisoning. You may need urgent medical attention. Taking more than the recommended dose of [product name] for a long period of time can cause serious health problems including effects on the heart, liver, and reproductive functions, as well as serious psychiatric problems. **b) While you are using it:** Things you must not do: Do not take more than the recommended dose of [product name]. Individuals who have taken more than the recommended dose for a long period of time may experience withdrawal symptoms lasting for weeks or months after abrupt discontinuation or a significant dose reduction of [product name]. These include: changes in mood and appetite, fatigue, insomnia, decreased sex drive as well as loss of function of the testes and ovaries. **Reference: Directive No. 19, 2017.** ***BPFK/PPP/07/25 (24) Jld. 1*** *Direktif Untuk Semua Produk Yang Mengandungi Testosteron: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Kesan Advers Susulan Penyalahgunaan dan Kebergantungan Ubat*
196.	**TETRACYCLINE SYRUP** The following boxed warning shall be included on the label and in the package inserts of products containing Tetracycline (syrup) **NOT TO BE GIVEN TO CHILDREN UNDER 12 YEARS OF AGE**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
197.	**THIOMERSAL** ***Note:*** Thiomersal is not allowed in ophthalmic preparations as preservative. The following statement shall be included on the label and package inserts of products containing thiomersal for preparations other than ophthalmic preparation: **WARNING** **'RISK OF SENSITIZATION IN RELATION TO THIOMERSAL AND OTHER PRESERVATIVES'** **Reference:** ***Bil. (34) dlm. BPFK/02/5/1.3*** *Penggunaan Thiomersal Dalam Persediaan Vaksin*
198.	**THROMBOLYTIC AGENTS** The following caution shall be disclosed prominently in the package inserts of products containing "systemic thrombolytic agent" in particular "the tissue plasminogen activators": **WARNINGS AND PRECAUTIONS** Severe bleeding such as intracranial haemorrhage may occur following administration of the drug, particularly in the elderly patients. The risk must be balanced against the potential benefit of thrombolysis. The following precautions need to be observed: Patients should be carefully observed for clinical signs during and following administration of the drug for early detection of bleeding. Frequent haematological tests such as blood coagulation tests are mandatory. To prevent bleeding at the site of centesis or other regions, caution must be exercised concerning procedures and management of arterial/ venus puncture. The use of heparin in conjunction with the thrombolytic agent for the purpose of prevention of reocclusion may increase the risk of intracranial haemorrhage. Close monitoring of patients is strongly recommended.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
199.	**TIAPROFENIC ACID** The following statement shall be included in the package inserts of products containing Tiaprofenic acid: **WARNINGS AND PRECAUTIONS** Urinary symptoms (bladder pain, dysuria, and frequency), haematuria or cystitis may occur. In certain exceptional cases, the symptoms have become severe on continued treatment. Should urinary symptoms occur, treatment with tiaprofenic acid must be stopped.
200.	**TOPIRAMATE** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) of products containing topiramate: **Package Insert** **a) Special Warnings and Precautions for Use** **Visual field defects** Visual field defects have been reported in patients receiving topiramate independent of elevated intraocular pressure. In clinical trials, most of these events were reversible following topiramate discontinuation, however some cases were not. In a large proportion of postmarketing case reports reversibility was unknown, but in cases where an outcome was reported, the majority were reversible. If visual problems occur at any time during topiramate treatment, consideration should be given to discontinuing the drug. **b) Warnings and Precautions:** Chronic, untreated metabolic acidosis may increase the risk of nephrocalcinosis **c) Adverse Effects/Undesirable Effects:** Renal and urinary disorders Very rare: Nephrocalcinosis Postmarketing data: Eye disorders Frequency “not known”: Uveitis

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Consumer Medication Information Leaflet (RiMUP) **a) Side Effects:** - There is a potential significant risk for metabolic acidosis that may have no symptoms and if left untreated may be associated with adverse effects on kidneys (e.g. kidney stone/ nephrocalcinosis). - Sudden changes in your eyesight (e.g. blurred vision) - Eye pain - Red eye **References:** **Directive No. 15, 2014.** ***Bil. (22) dlm. BPFK/PPP/07/25*** *Direktif Untuk Semua Produk Yang Mengandungi Topiramate: Amaran Berkaitan Risiko Gangguan Penglihatan* **Directive No. 13, 2019.** ***BPFK/PPP/07/25 (13) Jld.3*** *Direktif Untuk Semua Produk Yang Mengandungi Topiramate: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Penambahan Maklumat Keselamatan Berkaitan Nephrocalcinosis* **Directive No. 14, 2020.** ***NPRA.600-1/9/13(5)*** *Direktif Untuk Semua Produk Yang Mengandungi Topiramate: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Uveitis*
201.	**TRAMADOL** The following statements shall be included in the package insert and RiMUP of products containing Tramadol: **Package Insert** **a) Recommended Dosage:** Adults and adolescents (12 years and older) [Product name] is not approved for use in patients below 12 years old. Paediatric population The safety and efficacy of [product name] has not been studied in the paediatric population. Therefore, use of [product name] is not recommended in patients under 12 years of age. **b) Contraindications:** - Children younger than 18 years to treat pain after surgery to remove the tonsils and/or adenoids. - Adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea or severe lung disease, which may increase the risk of serious breathing problems.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	c) Warnings and Precautions: Paediatric population The safety and efficacy of [product name] has not been studied in the paediatric population. Therefore, use of [product name] is not recommended in patients under 12 years of age. Respiratory depression Administer [product name] cautiously in patients at risk for respiratory depression, including patients with substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression, as in these patients, even therapeutic doses of [product name] may decrease respiratory drive to the point of apnea. In these patients, alternative non-opioid analgesics should be considered. When large doses of tramadol are administered with anaesthetic medications or alcohol, respiratory depression may result. Respiratory depression should be treated as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures. Cytochromes P450 (CYP) 2D6 Ultra-Rapid Metabolism Some individuals may be CYP2D6 ultra-rapid metabolisers. These individuals convert tramadol more rapidly than other people into its more potent opioid metabolites O-desmethyltramadol (M1). This rapid conversion could result in higher than expected opioid-like side effects including life-threatening respiratory depression. The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese, Japanese and Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16-28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups. **d) Pregnancy and Lactation:** Pregnancy Tramadol has been shown to cross the placenta. There are no adequate and well-controlled studies in pregnant women. Safe use in pregnancy has not been established. [Product name] is not recommended for pregnant women. Lactation Approximately 0.1% of the maternal dose of tramadol is excreted in breast milk. In the immediate post-partum period, for maternal oral daily dosage up to 400 mg, this corresponds to a mean amount of tramadol ingested by breast-fed infants of 3% of the maternal weight-adjusted dosage. For this reason tramadol should not be used during lactation or alternatively, breast-feeding should be discontinued during treatment with tramadol. Discontinuation of breast-feeding is generally not necessary following a single dose of tramadol.

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	e) Adverse Effects/Undesirable Effects: Respiratory depression (rare) **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use [product name]** When you must not use it: - you are less than 12 years old. - you have slow or shallow breathing, or other breathing problems. - you are pregnant. - you are breastfeeding. **b) While you are using it:** Things to be careful of: - Tramadol is not to be used during breast-feeding. Small amounts of tramadol is excreted into breast milk. On a single dose it is usually not necessary to interrupt breast-feeding. If you have taken [product name] when you are breastfeeding, seek immediate medical attention if you notice your baby has any changes in their breathing (such as weak, difficult or fast breathing). **Reference: Directive No. 20, 2017.** ***BPFK/PPP/07/25 (25) Jld. 1*** *Direktif Untuk Semua Produk Yang Mengandungi Tramadol Dengan Maklumat Bagi Mengehadkan Penggunaan Tramadol Dalam Kalangan Kanak-Kanak dan Amaran Berkaitan Penggunaan Dalam Kalangan Ibu Mengandung dan Ibu Menyusu*
202.	**TRIMETAZIDINE** 1. Indication of products containing Trimetazidine shall be amended as follows: a) Indication of Trimetazidine for treatment of pectoris angina is limited to second-line add on therapy; and the indication in otology and ophthalmology field shall be removed. b) Permitted indication is ***trimetazidine is indicated in adults as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled by or intolerant to first-line antianginal therapies.*** 2. The following warning statement shall be included in the package inserts of products containing Trimetazidine: a) **Dosage and method of administration:** For products containing Trimetazidine 20mg: *The dose is one tablet of 20mg of trimetazidine three times a day during meals.*

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	The benefit of the treatment should be assessed after three months and trimetazidine should be discontinued if there is no treatment response. *Special populations* *Patients with renal impairment:* *In patients with moderate renal impairment (creatinine clearance [30-60] ml/min), the recommended dose is 1 tablet of 20mg twice daily, i.e., one in the morning and one in the evening during meals.* *Elderly patients:* *Elderly patients may have increased trimetazidine exposure due to age-related decrease in renal function. In patients with moderate renal impairment (creatinine clearance [30-60] ml/min), the recommended dose is 1 tablet of 20mg twice daily, i.e., one in the morning and one in the evening during meals. Dose titration in elderly patients should be exercised with caution.* For products containing Trimetazidine 35mg: *The dose is one tablet of 35mg of trimetazidine twice daily during meals.* *The benefit of the treatment should be assessed after three months and trimetazidine should be discontinued if there is no treatment response.* *Special populations* *Patients with renal impairment:* *In patients with moderate renal impairment (creatinine clearance [30-60] ml/min), the recommended dose is 1 tablet of 35mg in the morning during breakfast.* *Elderly patients:* *Elderly patients may have increased trimetazidine exposure due to age-related decrease in renal function. In patients with moderate renal impairment (creatinine clearance [30-60] ml/min), the recommended dose is 1 tablet of 35mg in the morning during breakfast. Dose titration in elderly patients should be exercised with caution.* b) **Contraindications:** - *Parkinson disease, parkinsonian symptoms, tremors, restless leg syndrome, and other related movement disorders* - *Severe renal impairment (creatinine clearance < 30ml/min).* c) **Warnings and precautions:** *Trimetazidine can cause or worsen parkinsonian symptoms (tremor, akinesia, hypertonia), which should be regularly investigated, especially in elderly patients. In doubtful cases, patients should be referred to a*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	neurologist for appropriate investigations. *The occurrence of movement disorders such as parkinsonian symptoms, restless leg syndrome, tremors, gait instability should lead to definitive withdrawal of trimetazidine.* *These cases have a low incidence and are usually reversible after treatment discontinuation. The majority of the patients recovered within 4 months after trimetazidine withdrawal. If parkinsonian symptoms persist more than 4 months after drug discontinuation, a neurologist opinion should be sought.* *Falls may occur, related to gait instability or hypotension, in particular in patients taking antihypertensive treatment.* *Caution should be exercised when prescribing trimetazidine to patients in whom an increased exposure is expected:* - *moderate renal impairment,* - *elderly patients older than 75 years old.* d) **Adverse Effects/ Undesirable Effects:** *Nervous system disorders:* *Frequency not known:* — *Parkinsonian symptoms (tremor, akinesia, hypertonia), gait instability, restless leg syndrome, other related movement disorders, usually reversible after treatment discontinuation.* **Reference: Directive No. 5, 2013.** ***Bil. (4) dlm.BPFK/PPP/07/25*** *Direktif Untuk Menghadkan Penggunaan Produk Mengandungi Trimetazidine dan Mengukuhkan Amaran Berkaitan Dengan Risiko Kesan Advers Simptom Parkinson Pada Sisip Bungkusan Semua Produk Trimetazidine*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
203.	**TRIPROLIDINE** The following statement shall be included on the label and in the package inserts of liquid oral products containing Triprolidine: **WARNING** When used for treatment of cough and cold: (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. **Reference:** ***Bil. (34) dlm. BPFK/PPP/01/03*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*
204.	**VARENICLINE** The following statement shall be included in the package inserts of products containing Varenicline: **WARNINGS AND PRECAUTIONS** Effect of smoking cessation: Smoking cessation, with or without pharmacotherapy has been associated with the exacerbation of underlying psychiatric illness (eg. depression). Care should be taken with patients with a history of psychiatric illness and patients should be advised accordingly. Depression, rarely including suicidal ideation and suicide attempt, has been reported in patients undergoing a smoking cessation attempt. **ADVERSE EFFECTS / UNDESIRABLE EFFECTS** Post marketing cases of MI, depression and suicidal ideation have been reported in patients taking varenicline. **Reference:** ***Bil. (83) dlm. BPFK/17/FV/28*** *Maklumat Dari European Medicines Agency (EMEA) Berkaitan Penggunaan Produk Champix (Varenicline) Untuk Rawatan Berhenti Merokok (Smoking Cessation)*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
205.	**Vascular Endothelial Growth Factor (VEGF) Inhibitors** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing VEGF inhibitors for systemic use (except application on eyes); **Package Insert** **a) Adverse Effects/ Undesirable Effects:** Vascular disorders Frequency "not known": aneurysms and artery dissections **Consumer Medication Information Leaflet (RiMUP)** **a) Side effects:** Frequency 'not known': An enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall (aneurysms and artery dissections). **Reference: Directive No. 10, 2021**. ***NPRA.600-1/9/13(20)*** *Direktif Untuk Semua Produk Yang Mengandungi Vascular Endothelial Growth Factor (VEGF) Inhibitors Untuk Kegunaan Sistemik (Kecuali Kegunaan Pada Mata): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Artery Dissections dan Aneurysms*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
206.	**VITAMIN K** 1. The following statement shall be included in the label and package insert of health supplement products containing Vitamin K as combined ingredients with other vitamins and minerals in oral preparation: **'Consult a healthcare practitioner if you are on anticoagulant/ blood thinner products.** 2. The following statement shall be included in the package inserts of products containing Vitamin K1 (phytomenadione) as single ingredient used intravenously: **WARNINGS AND PRECAUTIONS** Severe reactions, including fatalities, have occurred during and immediately after intravenous injection of Vitamin K1. Restrict intravenous use to emergency case. When intravenous administration is necessary, the rate of injection should not exceed 1mg per minute. **ADMINISTRATION**: In severe bleeding, or situations where other routes are not feasible, Vitamin K1 may be given by very slow intravenous injection, at a rate not exceeding 1mg per minute.
207.	**WARFARIN** The following statements shall be included in the package insert and RiMUP of products containing Warfarin: **Package Insert** **Caution** Topical preparations containing methyl salicylate should be used with care in patients on **Warfarin** and excessive usage is to be avoided as potentially dangerous drug interaction can occur. **Contraindications** Co-administration with miconazole oral gel (see Interactions).

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Warnings and Precautions: • Calciphylaxis is a rare syndrome of vascular calcification with cutaneous necrosis, associated with high mortality. The condition is mainly observed in patients with end-stage renal disease on dialysis or in patients with known risk factors such as protein C or S deficiency, hyperphosphatemia, hypercalcaemia or hypoalbuminaemia. Rare cases of calciphylaxis have been reported in patients taking warfarin, also in the absence of renal disease. In case calciphylaxis is diagnosed, appropriate treatment should be started and consideration should be given to stopping treatment with warfarin. • Co-administration with topical miconazole (see Interactions). **Interactions** The following drugs have been reported to potentiate the warfarin effect (increase INR): • Miconazole **Adverse Effects/ Undesirable Effects**: Skin and subcutaneous tissue disorders Frequency 'not known': Calciphylaxis **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **Side Effects**: Tell your doctor straight away if you have any of the following side effects : [...] A painful skin rash. On rare occasions warfarin can cause serious skin conditions, including one called calciphylaxis that can start with a painful skin rash but can lead to other serious complications. This adverse reaction occurs more frequently in patients with chronic kidney disease. **Before You Use [Product Name]** *<u>When you must not use it</u>*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Do not take [product name] together with miconazole oral gel *Before you start to use it* Some commonly used medicines and products that may interfere with [product name] include: • Miconazole **References:** **Directive No. 15, 2016.** ***BPFK/PPP/07/25 (1) Jld.1*** *Direktif Bagi Semua Produk Yang Mengandungi Warfarin Dengan Risiko Kesan Advers Calciphylaxis* **Directive No. 12, 2017.** ***BPFK/PPP/07/25 (17) Jld.1*** *Direktif Untuk Semua Produk Yang Mengandungi Warfarin: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Interaksi Ubat*

APPENDIX 21

SPECIAL CONDITIONS FOR REGISTRATION OF A PARTICULAR PRODUCT OR GROUP OF PRODUCTS

NO.	PRODUCTS
1.	**BLOOD PRODUCTS**
2.	**HUMAN GROWTH HORMONE** (Somatotropin, Somatropin)
3.	**KETOCONAZOLE**
4.	**MIDAZOLAM**
5.	**PARACETAMOL IN COMBINATION WITH CAFFEINE**
6.	**PARACETAMOL INTRAVENOUS INJECTION**
7.	**RETINOIDS INDICATED FOR THE TREATMENT OF SKIN DISEASES (ORAL)**
8.	**VACCINES**
9.	**COVID-19 VACCINES**

NO.	SPECIAL CONDITIONS/ REQUIREMENTS
1.	**BLOOD PRODUCTS** a) Each batch of product must comply with WHO requirements for the product. b) The following documents must be enclosed with each bath of the product imported into Malaysia: i. Batch Release Certificate from the relevant authority in the country of manufacture ii. Certificate confirming that the blood or plasma used in the production of the lot is tested and found to be negative for HIV antibody, HbsAg, and HCV, and that high-risk donors were excluded. iii. Certificate of analysis.
2.	**HUMAN GROWTH HORMONE** (Somatotropin, Somatropin) A proper record of product supplied stating the product name, product registration number, name, address and contact number of purchaser (prescriber) shall be kept and submitted to the Authority upon request.
3.	**KETOCONAZOLE** Oral products containing ketoconazole are restricted for hospital use only.
4.	**MIDAZOLAM** Products containing midazolam are restricted for use in government and private hospitals and specialist clinics only.
5.	**PARACETAMOL IN COMBINATION WITH CAFFEINE** a) For products containing a combination of paracetamol and caffeine: Dose unit of caffeine for adults is 65mg and maximum dose of caffeine is 520mg per day Dose unit for paracetamol is 500mg with the maximum dose of 4,000mg per day or 8 tablets daily. b) Products containing caffeine for pediatric patients are not allowed. c) Allowable packing size should not exceed 20 tablets/ capsules.
6.	**PARACETAMOL INTRAVENOUS INJECTION** Products containing paracetamol in the form of intravenous injection are restricted for hospital use only.
7.	**RETINOIDS INDICATED FOR THE TREATMENT OF SKIN DISEASES (ORAL)** a) The product registration holder shall ensure that the product shall only be sold or supplied to, and prescribed by: i. Dermatologists registered in the National Specialist Register; or

NO.	SPECIAL CONDITIONS/ REQUIREMENTS
	ii. Dermatologists serving in any government health facilities. b) The product registration holder shall submit a proper record containing the following information to the Authority upon request. i. Name of product; ii. Product registration number; iii. Date & quantity of product manufactured/ imported and supplied; and iv. Name, address & contact number of purchaser (prescriber). c) The prescriber shall keep and maintain proper patient records for audit purpose, if any. **Reference:** Directive No. 17, 2020. *NPRA.600-1/9/13 (8) Direktif Berkenaan Pindaan Syarat Pendaftaran Khas Bagi Produk Yang Mengandungi Oral Retinoid Yang Diindikasikan Untuk Rawatan Penyakit Kulit* (14 September 2020)
8.	**VACCINES** a) Each batch of the product must comply with WHO requirements for the product. b) A batch release certificate must be enclosed with each batch of the product imported into Malaysia.
9.	**COVID-19 VACCINES** a) The product registration holder shall ensure that the product shall only be sold or supplied to the government or other party authorized by the government only. **Reference:** *Keputusan Pihak Berkuasa Kawalan Dadah (PBKD) Berkenaan Penetapan Syarat Pendaftaran Bagi Vaksin COVID-19 Yang Diluluskan Pendaftaran Bersyarat Hanya Boleh Dijual Dan Dibekal Kepada Pihak Kerajaan Atau Pihak Yang Dibenarkan Oleh Kerajaan*, NPRA.600-1/9/7 (43) (10 March 2021)

APPENDIX 22

EDUCATIONAL MATERIALS

NO.	PRODUCTS
1.	**ORAL RETINOIDS INDICATED FOR TREATMENT OF SKIN DISEASES** 1.1 Patient Reminder Card 1.2 Prescriber Checklist/ Acknowledgement Form 1.3 Pharmacist Checklist **Reference: Directive No. 16, 2019**, ***BPFK/PPP/07/25(16) Jld.3***. *Direktif Untuk Semua Produk Yang Mengandungi Retinoid Yang Diindikasikan Untuk Rawatan Penyakit Kulit (Termasuk Topikal): Pengemaskinian Label, Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Bagi Memperkukuhkan Maklumat Keselamatan Berkaitan Kesan Teratogenik Serta Penyediaan Bahan-bahan Pengajaran (Educational Materials) Bagi Produk Yang Mengandungi Oral Retinoid Yang Diindikasikan Untuk Rawatan Penyakit Kulit* (27 September 2019)
2.	**SODIUM VALPROATE** 2.1 Patient Card 2.2 Annual Risk Acknowledgement Form 2.3 Guide for Healthcare Professionals 2.4 Guide for Female Patients/ Caregivers **References:** • **Directive No. 21, 2019**, ***BPFK/PPP/07/25(21) Jld.3***: *Direktif Untuk Semua Produk Yang Mengandungi Sodium Valproate: Pengukuhan Maklumat Keselamatan Pada Label, Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Berkaitan Risiko Kecacatan Kongenital dan Masalah Perkembangan Dalam Kalangan Bayi dan Kanak-kanak Yang Terdedah Kepada Penggunaan Sodium Valproate Semasa Dalam Kandungan Serta Penyediaan Bahan-bahan Pengajaran (Educational Materials) Bagi Produk Yang Mengandungi Sodium Valproate* (8 January 2020) • *NPRA website*

1. ORAL RETINOIDS INDICATED FOR TREATMENT OF SKIN DISEASES

1.1 Patient Reminder Card

Important information to know:

- [Product name] must not be taken during pregnancy. [Product name] can seriously harm an unborn baby if a pregnant woman takes it.
- If you become pregnant or think you might be pregnant, stop taking [product name] immediately and contact your doctor.
- If you have any questions or concerns about taking [product name], talk to your doctor or pharmacist.

What you must do:

- You must use effective contraception before, during and for 1 month* [*for acitretin: 3 years] after stopping treatment with [product name].
- You must not become pregnant while taking [product name], or for 1 month* [*for acitretin: 3 years] after stopping treatment.
- You must attend regular follow-up visits and have regular pregnancy testing.

Reminder for Men and Women

Do not share this medication with anybody and return any unused capsules back to the pharmacy. You should not donate blood during treatment with this medicine and for 1 month* [*for acitretin: 3 years] after stopping treatment.

1.2 Prescriber Checklist/ Acknowledgement Form

PRESCRIBER CHECKLIST/ ACKNOWLEDGEMENT FORM FOR PRESCRIBING [PRODUCT NAME] TO FEMALE PATIENTS

The potential for pregnancy must be assessed for all female patients prescribed [product name].

A woman has a potential for pregnancy if one of the following applies:

Is a sexually mature woman who:

1. has not had a hysterectomy or bilateral oophorectomy
2. is not in a natural postmenopause for a minimum of 24 consecutive months (i.e., menstruated at a certain point in the last 24 consecutive months).

Before initiating [product name] in a female patient, the following checklist is to be completed by the prescriber and kept with the patient notes to document compliance with the [product name] Pregnancy Prevention Programme. After completion, a copy of this document should be given to the patient.

[Product name] belongs to the retinoid class of drugs that cause severe birth defects. Foetal exposure to [product name], even for short periods, presents a high risk of congenital malformations. [Product name] is therefore strictly contraindicated in women of childbearing potential, unless all conditions in the [product name] Pregnancy Prevention Programme are fulfilled.

As the prescriber, you must make sure that the risk of serious harm from drug exposed pregnancy is fully understood by all female patients before treating them with [product name].

This checklist should also be used in all follow-up visits with women of childbearing potential.

Please use the patient reminder card to support your discussion with the patient.

Is the patient a woman of childbearing potential? If No, go to Section 4.

Women of childbearing potential: **Review the below statements**, explain them to the patient and record confirmation of this and acknowledgment from the patient in this form. If the answer to any of these questions is NO, [product name] must not be prescribed.

	Prescriber confirm: I have explained this to my patient		**Patient confirm: I have understood this**	
Is the patient suffering from a severe form of acne, which is resistant to standard therapies? [for acitretin: Is the patient suffering from a severe form of psoriasis or severe disorder of keratinization ?]	Yes ☐	No ☐	Yes ☐	No ☐
1. Teratogenicity				
The patient understands that [product name] belongs to a class of drugs (retinoids) known to cause severe birth defects and that they must not get pregnant whilst taking it. [Product name] also increases the risk of miscarriage when taken during pregnancy.	Yes ☐	No ☐	Yes ☐	No ☐
2. Contraception				
The patient understands that she must consistently and correctly use at least 1 highly effective method of contraception (i.e. a user-independent form such as an intra-uterine device or implant) or 2 complementary methods of birth control (i.e. user-dependent forms such as oral contraceptive and barrier method) before and during treatment.	Yes ☐	No ☐	Yes ☐	No ☐
The patient understands that the risk persists even after the medication is stopped and that she must not get pregnant within 1 month* [*for acitretin: 3 years] after stopping treatment.	Yes ☐	No ☐	Yes ☐	No ☐
The patient has received advice on contraception which is appropriate for her and has committed to using it throughout the risk period.	Yes ☐	No ☐	Yes ☐	No ☐
The patient is aware of the risk of contraceptive failure.	Yes ☐	No ☐	Yes ☐	No ☐

	Prescriber confirm: I have explained this to my patient		**Patient confirm: I have understood this**	
3. Pregnancy Testing & Ideally Monthly Prescriptions				
The first prescription for [product name] can only be given after the patient has had one negative medically supervised pregnancy test. This is to make sure she is not already pregnant before starting treatment.	Yes ☐	No ☐	Yes ☐	No ☐
Patient understands that in order to support regular follow up, including pregnancy testing and monitoring, ideally the prescription be limited to 30 days.	Yes ☐	No ☐	Yes ☐	No ☐
Patient understands the need for and agrees to pregnancy testing before, during and after treatment.	Yes ☐	No ☐	Yes ☐	No ☐
Patient understands the need to do a pregnancy test 1 month* after stopping treatment [*for acitretin: 1-3 monthly intervals throughout treatment and also for a period of 3 years after stopping treatment] because the drug stays in the body for 1 month* [*for acitretin: 3 years] after the last dose and can damage an unborn baby if pregnancy occurs.	Yes ☐	No ☐	Yes ☐	No ☐
The contraceptive methods and pregnancy test results were recorded in the patient's medical records.	Yes ☐	No ☐	Yes ☐	No ☐
The patient knows to contact their doctor if they have unprotected sex, miss their period, become pregnant, or suspect that they have become pregnant during the risk period.	Yes ☐	No ☐	Yes ☐	No ☐
If pregnancy occurs, treatment must be stopped and the patient should be referred to an expert physician specialised or experienced in teratology for advice.	Yes ☐	No ☐	Yes ☐	No ☐
The patient has received a reminder card and copy of this form.	Yes ☐	No ☐	Yes ☐	No ☐

	Prescriber confirm: I have explained this to my patient		**Patient confirm: I have understood this**	
4. Other Precautions				
Patient understands that [product name] has been prescribed to her only and must not be shared with others.	Yes ☐	No ☐	Yes ☐	No ☐
Patient understands that she must not donate blood during treatment with [product name] and for one month* [*for acitretin: 3 years] after discontinuation due to the potential risk to the foetus of a pregnant transfusion recipient.	Yes ☐	No ☐	Yes ☐	No ☐

1.3 PHARMACIST CHECKLIST - GUIDANCE FOR DISPENSING [PRODUCT NAME]

[Product name] belongs to the retinoid class of drugs that cause severe birth defects. Foetal exposure to [product name], even for short periods of time, presents a high risk of congenital malformations and miscarriage.

[Product name] is therefore strictly contraindicated during pregnancy and in women of childbearing potential, unless all conditions in the Pregnancy Prevention Programme are fulfilled.

Female patient must use effective contraception before, during and for 1 month* [*for acitretin: 3 years] after stopping treatment with [product name].

If you are aware that a female patient has become pregnant within 1 month* [*for acitretin: 3 years] of stopping [product name], she should be referred to her prescribing doctor.

As the pharmacist, you should only dispense [product name] after checking the following information:

For women of child-bearing potential:	
In order to support regular follow up, including pregnancy testing and monitoring, the prescription for [product name] ideally be limited to a 30-day supply.	
All patients should be instructed:	
Never to give the [product name] to another person.	
To return any unused capsules to their pharmacist at the end of treatment.	
Not to donate blood during [product name] therapy and for 1 month* [*for acitretin: 3 years] after discontinuation due to the potential risk to the foetus of a pregnant transfusion recipient.	

2. SODIUM VALPROATE

2.1 Patient Card

PATIENT CARD

Muka Hadapan Kad

Patient Card for Sodium valproate [Product Name]: Contraception and Pregnancy

What You Must Know

- Sodium valproate is an effective medicine to treat epilepsy or bipolar disorder
- Sodium valproate can cause serious harm to your baby when taken during pregnancy
- Always use effective contraception throughout the entire duration of treatment

Note:

- This also applies to all girls and women taking sodium valproate who could become pregnant
- Keep this card safe so you always know what to do

Muka Belakang Kad

Patient Card for Sodium valproate [Product Name]: Contraception and Pregnancy

What You Must Do

- Read the package leaflet carefully before use
- Never stop taking sodium valproate unless your doctor tells you as your condition may become worse
- If you are thinking of getting pregnant, CONTINUE taking your sodium valproate and contraception until you talk to your doctor.
- If you think you are pregnant, CONTINUE taking sodium valproate. Make an urgent appointment with your doctor.

Note:

- This also applies to all girls and women taking sodium valproate who could become pregnant
- Keep this card safe so you always know what to do

2.2 Annual Risk Acknowledgement Form

ANNUAL RISK ACKNOWLEDGEMENT FORM

PART A. TO BE COMPLETED AND SIGNED BY THE PRESCRIBER

Patient Name : _____

MRN / IC No. : _____

Address : _____

For girls and women of childbearing age treated with sodium valproate <Product Name>

Read, complete and sign this form during a visit with the prescriber: at treatment initiation, at the annual visit, and when a woman plans a pregnancy or is pregnant.

Name of patient or care-giver: _____

I confirm that the above-named patient needs sodium valproate because:

- ☐ this patient does not respond adequately to other treatments or
- ☐ this patient does not tolerate other treatments
- ☐ that this patient is already stable on …… dose and she is reluctant to change to other medication.
- ☐ Other reason (to specify) ……..

I have discussed the following information with the above-named patient or care-giver:

- ☐ The overall risk to fetus and children whose mothers are exposed to sodium valproate during pregnancy are:
  - an approximately 10% chance of birth defects and
  - up to 30 to 40% chance of a wide range of early developmental problems that can lead to learning difficulties.
- ☐ Sodium valproate should not be used during pregnancy (except in rare situations for epileptic patients that are resistant or intolerant to other treatments)
- ☐ The need for regular (at least annually) review and the need to continue sodium valproate treatment by the prescriber.
- ☐ The need for negative pregnancy test at treatment initiation and as required thereafter (if child bearing age).
- ☐ The need for an effective contraception without interruption during the entire duration of treatment with sodium valproate (if childbearing age).
- ☐ The need to arrange an appointment with her doctor as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception and before contraception is discontinued.
- ☐ The need to contact her doctor immediately for an urgent review of the treatment in case of suspected or inadvertent pregnancy.
- ☐ In case of pregnancy, I confirm that this pregnant patient:
  - received the lowest possible effective dose of sodium valproate to minimise the possible harmful effect on the unborn
  - is informed about the possibilities of pregnancy support or counselling and appropriate monitoring of her baby if she is pregnant.

Name of Prescriber: _____ Signature: _____ Date: _____

Part A and B shall be completed: all boxes shall be ticked, and the form signed by the prescriber. This is to make sure all the risks and information related to the use of sodium valproate during pregnancy have been understood. Part A – to be kept by the prescriber

ANNUAL RISK ACKNOWLEDGEMENT FORM

PART B. TO BE COMPLETED BY PRESCRIBER AND SIGNED BY THE PATIENT OR CAREGIVER

Patient name : _____

MRN / ICNo. : _____

Address : _____

For girls and women of childbearing age treated with sodium valproate <Product Name>

Read, complete and sign this form during a visit with the prescriber: at treatment initiation, at the annual visit, and when a woman plans a pregnancy or is pregnant.

I have discussed the following with my doctor and understand:

- ☐ Why I need sodium sodium valproate rather than other medicine
- ☐ I have decided to continue with the treatment after being advised on the risk
- ☐ That I should visit the prescriber regularly (at least annually) to review whether sodium valproate treatment remains the best option for me
- ☐ The overall risk to fetus and children whose mothers took sodium sodium valproate during pregnancy are:
  - an approximately 10% chance of birth defects and
  - up to 30 to 40% chance of a wide range of early developmental problems that can lead to significant learning difficulties

- ☐ Why I need a negative pregnancy test at treatment initiation and if needed thereafter (if child bearing age)
- ☐ That I must use an effective contraception without interruption during the entire duration of my treatment with sodium valproate (if childbearing age).
- ☐ We discussed the possibilities of effective contraception or we planned a consultation with a professional who is experienced in advising on effective contraception.
- ☐ The need for regular (at least annually) review and the need to continue sodium valproate treatment by the prescriber.
- ☐ The need to consult my doctor as soon as I am planning to become pregnant to ensure timely discussion and switching to alternative treatment options prior to conception, and before contraception is discontinued.
- ☐ That I should request an **urgent** appointment if I think I am pregnant
- ☐ In case of a pregnancy, I have discussed the following with my doctor and understand:
  - The possibilities of pregnancy support or counselling
  - The need to appropriate monitoring of my baby if I am pregnant

Name of Patient/Caregiver: _____ Signature: _____ Date: _____

Name of Prescriber : _____ Signature: _____ Date: _____

Part B shall be completed: all boxes shall be ticked, and the form signed by prescriber and the patient. This is to make sure all the risks and information related to the use of sodium valproate during pregnancy have been understood.

Part B - to be given to patient

- a copy to be kept by the prescriber

2.3 Guide for Healthcare Professionals

GUIDE FOR HEALTHCARE PROFESSIONALS

RISK OF CONGENITAL MALFORMATIONS AND NEURODEVELOPMENTAL DISORDERS FOLLOWING USE OF SODIUM VALPROATE

Note: This guide is to inform you of important information and strengthened warnings related to this risk

BACKGROUND INFORMATION: SAFETY DATA

1. Congenital Malformations

Data derived from two meta-analysis (including registries and cohort studies) have shown that 10.73% (95% Confidence Interval: 8.16-13.29%)[1] to 10.93% (95% Confidence Interval: 8.91-13.13%) of children of epileptic women exposed to sodium valproate monotherapy during pregnancy suffer from congenital malformations)[2]. This represents a greater risk of major malformations than for the general population, for whom the risk is equal to about 2-3%[1]. Available data show that the risk is dose dependent.The risk is greatest at higher doses (above 1g daily). A threshold dose below which no risk exists cannot be established based on available data.

The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body system.

2. Developmental Disorders

Exposure to sodium valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk regardless of when during the pregnancy exposure occurs cannot be excluded.

Studies[3-6] in preschool children show that up to 30-40% of children with a history of sodium valproate exposure in utero experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Available data show that children with a history of sodium valproate exposure in utero are at increased risk of autistic spectrum disorder (an approximately three-fold) and childhood autism (an approximately fivefold) compared with the general study population[6].

Limited data suggests that children with a history of sodium valproate exposure in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD)[7].

RECOMMENDATIONS

1. The use of sodium valproate had been restricted in pregnancy as such:
   - In epilepsy
     - sodium valproate is contraindicated unless there is no suitable alternative treatment.
   - In bipolar disorder
     - sodium valproate is contraindicated in pregnancy.
2. The use of sodium valproate in women of childbearing potential is contraindicated unless patient had been assessed and counselled appropriately on the risks associated with sodium valproate.
3. Treatment should only be initiated if other treatments ineffective or not tolerated.
4. Treatment should only be initiated after pregnancy has been excluded (negative pregnancy test).
5. The benefit and risk should be carefully reconsidered at regular treatment reviews. Preferably, sodium valproate should be prescribed as monotherapy and at the lowest effective dose. A prolonged release formulation is preferred to avoid high peak plasma concentrations. The daily dose should be divided into at least two single doses
6. Carry out annual review and ad-hoc treatment review when required. The benefit and risk should be carefully reconsidered during every treatment review.
7. In the case where sodium valproate must be used during pregnancy, prenatal monitoring is recommended to detect any malformations.

COUNSELLING POINT

- advise patient/ caretaker on the risk of congenital malformations and neurodevelopmental disorders associated with sodium valproate. Inform patient also about the risks of untreated seizure or bipolar disorder.
- advise patient to use effective contraception without interruption throughout the entire duration of sodium valproate treatment
- advise patient not to stop treatment abruptly and to urgently contact the doctor when planning for pregnancy or in the case of suspected pregnancy.
- ensure that patient has received educational materials such as patient card and patient guide that has been provided by the supplier of sodium valproate.

References

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2.4 Guide for Female Patients/ Caregivers

GUIDE FOR FEMALE PATIENTS/ CAREGIVERS

RISK OF BIRTH DEFECT & DEVELOPMENTAL PROBLEM FOLLOWING USE OF SODIUM VALPROATE

This information in this leaflet is for women and girls who are prescribed with sodium valproate and are able to get pregnant (child-bearing age). Please read this leaflet carefully and talk to your doctor of pharmacist if you have any question

KEY POINTS:

- Sodium valproate is an effective medicine used to treat seizure (epilepsy) and bipolar disorder.
- Sodium valproate can seriously harm an unborn child when taken during pregnancy and should not be taken by women and girls unless no other medicine works.
- Never stop taking sodium valproate unless your doctor tells you to stop.
- Always use contraception and do not stop using as long as you are taking sodium valproate.
- See your doctor at once if you are planning pregnancy or if you suspect that you are pregnant. Do not stop taking sodium valproate.
- Please make sure that you receive the patient educational materials such as patient card and patient guide from your healthcare provider.

What you must do if you are being prescribed sodium valproate:

- For women who are able to get pregnant (of child-bearing age):
  - When taking sodium valproate, always use **reliable contraception** and never stop using it so you do not have unplanned pregnancy as long as you are taking sodium valproate
  - Tell your doctor at once if you think you may be pregnant or know you are pregnant.
  - Never stop taking sodium valproate unless your doctor tells you to as your condition may become worse

- If you are thinking to get pregnant:
  - Arrange urgent appointment with your doctor if you plan to get pregnant or if you suspect that you are pregnant. Do not stop taking sodium valproate and contraception until you have seen your doctor.

You can help by reporting any side effects that you may get directly to the National Pharmaceutical Regulatory Agency (NPRA) through the website *https://www.npra.gov.my* (Consumer→Consumer Reporting of Side effects To Medicines or Vaccines→ConSERF).

INFORMATION ON THE RISKS TO THE UNBORN CHILD

- Sodium valproate can be harmful to unborn children when taken by a woman during pregnancy.
- Sodium valproate can cause serious birth defects and can affect the way in which the child develops as it grows. Birth defects include spina bifida (where the bones of the spine are not properly developed); facial and skull malformations; heart, kidney, urinary tract and sexual organ malformations; and limb defects.
- Because sodium valproate has been used for many years, we know that in women who take sodium valproate, around 10 babies in every 100 will have birth defects. This compares to 2-3 babies in every 100 born in the general population.
- It is estimated that up to 30-40% of preschool children whose mothers took sodium valproate during pregnancy may have problems with **early childhood development**. Children affected can be slow to walk and talk, intellectually less able than other children, and have difficulty with language and memory. In addition, disorders which affect the way a child communicates and interacts with others, for example autism, are more often diagnosed in children exposed to sodium valproate.

APPENDIX 23

PATIENT DISPENSING PACK FOR PHARMACEUTICAL PRODUCTS

Contents:

1. Purpose
2. Objectives
3. Definition
4. Benefits
5. Criteria for Implementation of Patient Dispensing Pack
6. Exempted Products
7. Other Considerations for Implementation
8. Implementation Timeline
9. Conclusions

1. PURPOSE

To provide guidance on the implementation of patient dispensing pack or original dispensing pack for pharmaceutical products in Malaysia.

2. OBJECTIVES

Improve patient safety by:

- maintaining product integrity;
- preventing unnecessary exposure of the product;
- avoiding product contamination due to handling, especially in non-GMP premise; and
- having fewer steps in the dispensing process to minimise errors and improve efficiency.

3. DEFINITION

Patient dispensing pack or original dispensing pack is a ready-to-dispense pack with sufficient quantity equivalent to an amount not more than one month supply or per treatment for one patient's use.

4. BENEFITS

Key benefits include:

- Improving medication adherence by ensuring that patients know how to take their medications and the importance of their medicines
- Facilitating identification of the medicine with manufacturer's information
- Providing complete instructions on how to take the medicine
- Ensuring the stability of the product because the original packaging will maintain the integrity of the pack
- Preventing mix-ups (or contamination) during repacking and dispensing
- Facilitating recall of products because the required information can only be found on the original packaging. The original packaging will have the batch number and expiry date information

5. CRITERIA FOR IMPLEMENTATION OF PATIENT DISPENSING PACK

- The patient dispensing pack size should be based on the medication, intended use, recommended dosage and dosage form sufficient for one month supply or per treatment for one patient's use.
- This requirement does not apply for blister or strip pack.
- The maximum permitted supply is one month but may be less depending on the intended use of the medication.
- The Product Registration Holder (PRH) is responsible for justifying the proposed patient dispensing pack size based on these criteria as the dosing regimen for certain medications may equate to large amounts of tablets/ capsules. The justification provided should also define one month supply, whether for 28, 30 or 31 days.
- Blisters or strip packs are strongly recommended for solid oral dosage forms (e.g. tablets and capsules). Bulk loose pack for supply of more than one month is not permitted unless properly justified by the PRH.
- Oral chemotherapeutics in tablet or capsule must be packed in blisters to reduce personnel exposure and presumable risk to minimise the toxic effect of the chemotherapeutics.

6. EXEMPTED PRODUCTS

These requirements do not apply to the following products:

- Injectables, eye, ear and nasal drops, suppositories and pessaries
- Products for export only (FEO)
- Drug where the risk of issuing more than the amount required by the patient outweigh the benefits of the patient dispensing pack. E.g. products containing substances with potential for abuse or cytotoxic agents where precise dosing are required.
- Drugs where the dosing needs to be tailored according to patient's body weight. E.g. drugs used in oncology, HIV, etc.
- Medically critical products and hospital packs for rare diseases with very low volumes where it is not viable to produce special packs for a single market
- Products sold in devices with a fixed number of doses
- Situations where a patient dispensing pack is not appropriate will be considered on a case-to-case basis.

7. OTHER CONSIDERATIONS FOR IMPLEMENTATION

VARIATION APPLICATIONS

- Change in patient pack size (regardless of whether a new pack type is involved) shall be submitted to the Variation Unit, Centre of Product & Cosmetic Evaluation (PPPK).

- The following supporting documents are required:
  a. Justification for the new pack size and/or type;
  b. Accelerated stability data (3 or 6 months) and stability report for new pack types; and
  c. Commitment to provide complete real time stability data and report when available.

- Lists of products with recommended maximum pack sizes for oral liquid preparations and dermatological preparations are presented in **Table 1** and **Table 2** respectively.

- For tablets and capsules in loose pack, the maximum pack size will depend on the highest dosage and frequency per patient's treatment or one month supply.

8. IMPLEMENTATION TIMELINE

- Implementation of patient dispensing pack has been conducted in a phased manner to ensure smooth transition and prevent supply disruption to patients. This implementation was made effective on 1 March 2008 on a voluntary basis and mandated on 1 September 2008.

- All products, whether imported or locally manufactured, manufactured from 1 September 2008 regardless whether it is imported or locally manufactured will need to conform to the principles of this guide.

9. CONCLUSIONS

Patient Dispensing Pack is convenient, safe and improves the quality of dispensed medicines. It increases efficiency in dispensing and improves patient safety by reducing the risk and possibility of error. It also reduces drug waste and promotes better use of resources.

TABLE 1:

Recommended Maximum Pack Sizes for Pharmaceutical Oral Liquid Preparation

ATC Code	Recommended Maximum Pack Sizes
R05 Cough & cold preparation R05A Cold preparation R05C Antitussives R05D Expectorants	120ml (except for Pholcodine –90ml)
R06A Antihistamines systemic	120ml (except for Hydroxyzine HCl Syrup - 200ml)
R03 Anti-asthma & COPD products R03A Beta2 stimulants R03B Xanthines (theophyllines) R03C Non-steroidal respiratory anti-inflammatory (ketotifen)	120ml (except for Procaterol - 250ml)
N02B Non-narcotic analgesics	120ml
M01A Antirheumatics non-steroid	120ml
H02 Systemic corticosteroids H02A Plain corticosteroids	120ml
M06A Anti-inflammatory enzymes	500ml
A02A Antacid antiflatulents **A02B Antiulcerants**	250ml
A06A Laxatives	120ml (except for Lactulose - 500ml)
A03 Functional GI disorder drugs A03A Antispasmodic A03E Other GI combinations (Colimix) A03F Gastroprokinetics (Metoclopramide, Motilium) A07 Antidiarrhoea	120ml
A04A Antiemetic + Antinauseants **N07C Antivertigo products**	120ml
N03A Antiepileptics	250ml (Except for Sodium Valproate Syrup - 300ml)

ATC Code	Recommended Maximum Pack Sizes
N06A Antidepressant & Mood stabilizer **N06D Anti Dementia** **N07D Anti-Alzheimer products** **N05A Antipsychotics**	250ml
P01B Antihelmintics	60ml
N05C Tranquillizers/ Anxiolytics	250ml
A05B Hepatic protector – lipotropics	150ml
J05 Antivirals for systemic use J05B Antivirals excluding Anti-HIV J05C HIV antivirals	250ml
J01 Antibiotics systemic J01A Tetracyclines & combination J01B Chloramphenicols combinations J01C1 Oral broad spectrum Penicillins J01D1 Oral Cephalosporins J01E Trimethoprim combinations J01F Macrolides & similar type J01H Medium & narrow spectrum penicillins J01X Other antibiotics **J02A Systemic Antifungals Agents**	120ml
N06D Nootropics **N06E Neurotonics & Miscellaneous**	125 ml
G01A1 Trichomonacides	120ml

TABLE 2:

RECOMMENDED MAXIMUM PACK SIZES FOR PHARMACEUTICAL DERMATOLOGICAL PREPARATION

ATC Code	Recommended Maximum Pack Sizes
D01A Antifungals for topical use	Liquid preparation - 250ml Others - 60g
D02A Emollients and protectives	Non poisons (liquid preparation) - 250ml Others - 60g (500g for emollients) Except D02AC Soft paraffin and fat products and D02AX Other emollients and protectives (Aq. Cream) - 500g
D03 Preparations for treatment of wounds and ulcers	500ml to 1L ***Notes:*** ▪ Chlorhexidine gluconate aqueous 1L ▪ Povidon 10% 500ml ▪ Povidon-iodine 1L ▪ Dermacyn 500ml ▪ Hydrogen peroxide 1L ▪ Prontosan 500ml ▪ Octenisan 500ml ▪ Acetic acid 500ml ▪ Cetrimide 500ml
D04A Antipruritics, anesthetics, etc. Except D04AA Antihistamines for topical use (not allowed for registration)	Liquid –250ml Others – 60g

ATC Code	Recommended Maximum Pack Sizes
D05A Antipsoriatics for topical use	Liquid –500ml (with a dispenser). Others –*500g Bar –100g * ***Notes:*** ▪ Tar Preparations ▪ Coal Tar Ointment/ Solution ▪ Liquor Picis Carbonis (LPC) 500g ▪ Dithranol Ointment 500g ▪ Cocois Co Lotion 500ml
D06A Antibiotics for topical use	20g Except D06BB Antivirals - 10g D06B A 01 Silver Sulphadiazine for management of burns - 500g
D07A Corticosteroids, plain D07AA Corticosteroids, weak (group I) D07AB Corticosteroids, moderately potent (group II) D07AC Corticosteroids, potent (group III) D07AD Corticosteroids, very potent (group IV)	 D07AA –100g to **500g D07AB –50g to **500g D07AC –15g to 100g D07AD –15g to 100g ** ***Note:*** Pack size of 500g is for hospitals and skin specialist clinics use.

ATC Code	Recommended Maximum Pack Sizes
D07C Corticosteroids, combinations with antibiotics D07CA Corticosteroids, weak, combinations with antibiotics D07CB Corticosteroids, moderately potent, combinations with antibiotics D07CC Corticosteroids, potent, combinations with antibiotics D07CD Corticosteroids, very potent, combinations with antibiotics	D07CA - 100g D07CB - 50g D07CC - 15g D07CD - 15g
D08A Antiseptics and disinfectants	Liquid antiseptics/ disinfectants - 1Litre Others - 60g
D10A Anti-acne preparations for topical use Except for D10AA Corticosteroids, combinations for treatment of acne	Liquid preparation - 250ml (recommended to be used with a dispenser) Bar - 100g All others - 60g
D11AF Wart and anti-corn preparations	15ml
M02A Topical products for joint and muscular pain	Liquid – 250ml Others, – 60g
D11AX11 Hyperpigmentation	60g

References:

i. *Bil. (16) dlm. BPFK/02/5/1.3*
Kawalan Saiz Pek Persediaan Ubat Batuk Mengandungi Pholcodine (13 October 2003)

ii. *Bil. (22) dlm. BPFK/02/5/1.3*
Lanjutan Tempoh Untuk Menarik Balik Saiz Pek Persediaan Ubat Batuk Mengandungi Pholcodeine Yang Melebihi 90mL Dari Pasaran (7 November 2003)

iii. *Bil. (21) dlm. BPFK/02/5/1.3*
Kawalan Penetapan Saiz Pek Maksima Bagi Semua Persediaan Ubat Batuk (7 November 2003)

iv. *Bil. (24) dlm. BPFK/02/5/1.3*
Pindaan Kepada Kawalan Penetapan Saiz Maksima Bagi Semua Persediaan Ubat Batuk (8 March 2004)

v. *Bil. (1) dlm. BPFK/02/5/1.4*
Perlaksanaan Konsep Pek Saiz Pesakit (Patient Pack Size) bagi Produk Farmaseutikal (20 February 2008)

vi. *Bil. (4) dlm. BPFK/PPP/01/03 Jld. 1*
Direktif Justifikasi Untuk Perubahan Pek Saiz Pesakit Untuk Penyakit Kulit Tertentu Bagi Produk-produk Dermatologi (14 December 2010)

APPENDIX 24

APPEAL

As stipulated under Regulation 18, CDCR 1984, any person aggrieved by the decision of the Authority or the Director of Pharmaceutical Services, may make a written appeal to the Minister of Health Malaysia.

All notice of appeals shall be made **within fourteen (14) days** from the date of notification by the Authority;

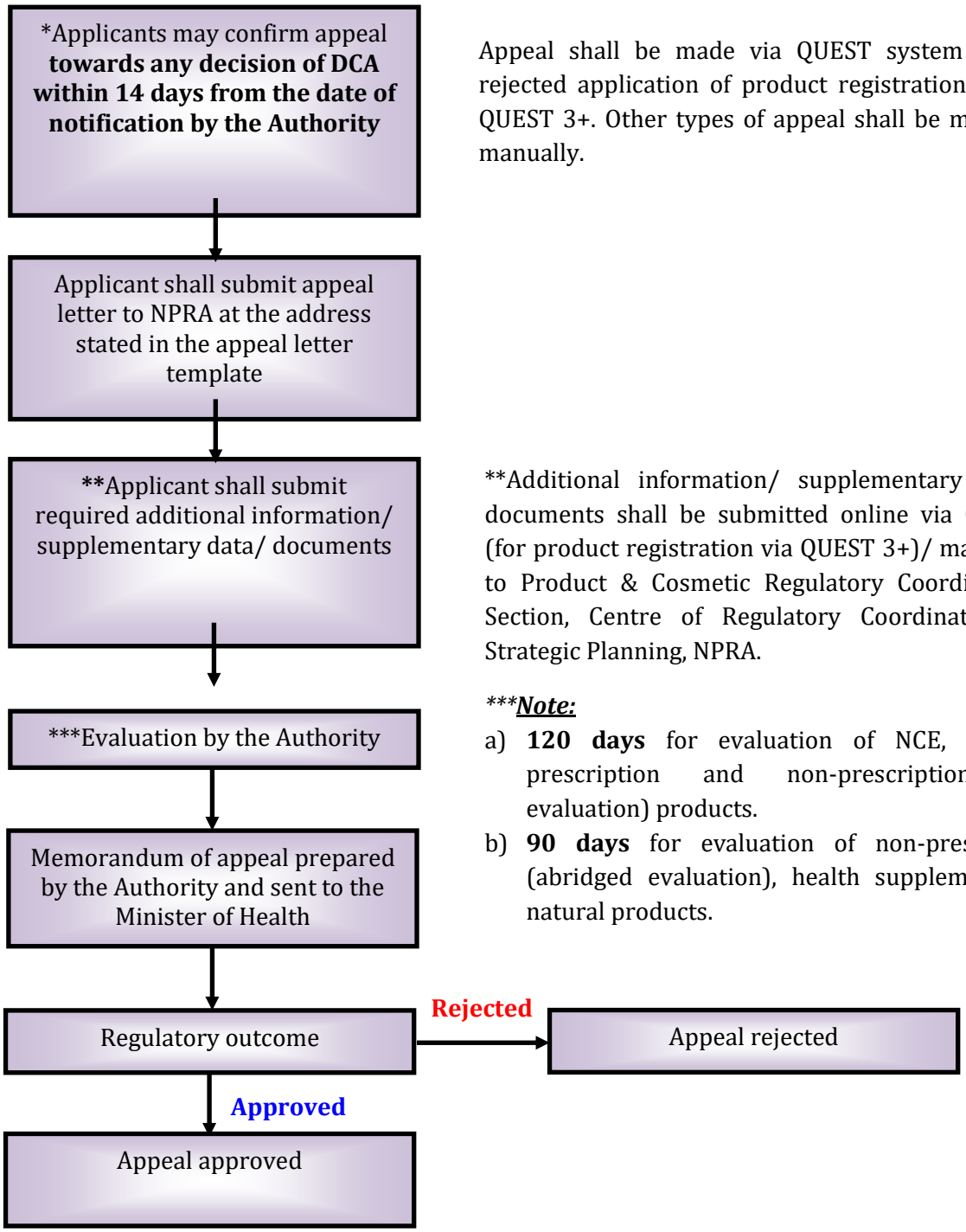
- A period of 60 days from the date of appeal confirmation is given for submission of any additional information/ supplementary data/ documents for all product categories.

- The appeal shall not be considered if all the required information is not submitted within the specified time frame given. **Any request for extension of this period shall not be considered.**

- Any decision of the Minister made on an appeal shall be final.

The appeal for rejected applications of product registration shall be submitted via the online QUEST system ONLY. Other types of appeal shall may be submitted manually.

THE PROCESS OF APPEAL



Appeal shall be made via QUEST system for rejected application of product registration via QUEST 3+. Other types of appeal shall be made manually.

**Additional information/ supplementary data/ documents shall be submitted online via QUEST (for product registration via QUEST 3+)/ manually to Product & Cosmetic Regulatory Coordination Section, Centre of Regulatory Coordination & Strategic Planning, NPRA.

****Note:***

a) **120 days** for evaluation of NCE, Biologic, prescription and non-prescription (full evaluation) products.

b) **90 days** for evaluation of non-prescription (abridged evaluation), health supplement and natural products.

TEMPLATE FOR AN APPEAL LETTER

***LETTERHEAD* SYARIKAT PEMEGANG PENDAFTARAN PRODUK**
Nama dan alamat pemegang

Tarikh:

Y. B. Menteri Kesihatan Malaysia
d/a Bahagian Regulatori Farmasi Negara
Kementerian Kesihatan Malaysia
Lot 36, Jalan Universiti,
46200 Petaling Jaya
(u.p. Setiausaha PBKD)

Y. B.,

PERATURAN 18 – RAYUAN TERHADAP PENOLAKAN PERMOHONAN PENDAFTARAN

NAMA PRODUK	:	Sila nyatakan nama produk (*Please state the product name*)
NO. RUJUKAN	:	Sila nyatakan nombor pendaftaran produk (*Please state the product reference number*)

Dengan segala hormatnya, pihak kami ingin membuat rayuan terhadap penolakan permohonan produk seperti di atas.

2. Alasan – alasan rayuan serta data tambahan/ maklumat akan dihantar kepada pihak Y.B. dalam tempoh 60 hari dari tarikh pengesahan penerimaan rayuan oleh pihak Y.B.

Sekian, terima kasih.

Yang benar,

Tandatangan Wakil Pemegang

(NAMA WAKIL PEMEGANG)
Jawatan Wakil Pemegang

APPENDIX 25

GUIDELINE FOR THE SUBMISSION OF PROTOCOL OF ANALYSIS (POA)

This guideline consists of general and specific requirements for the POA submission. The general requirements are referred for POA content whilst details of specific requirements are illustrated according to the test category.

1. GENERAL REQUIREMENTS

a) The POA shall be written in *Bahasa Malaysia* or English only.

b) The POA shall contain the following information:

i) Name of product;
ii) Name and address of manufacturer;
iii) Name, signature and designation of authorized person;
iv) Effective date and Review date.

c) The POA shall comply with the following requirements :

i) To provide updated testing methods, shelf-life specifications and certificate of analysis for the intended product to be registered.
ii) References used must be clearly stated.
iii) The latest version of British Pharmacopoeia (BP) and United States Pharmacopeia (USP) shall be used as the main references.
iv) All tests and its specification listed in BP and/or USP in General Monographs and Specific Monographs shall be the minimum requirement. However, a specific testing method for quantitative analysis shall be accepted.
v) All test specifications set by the manufacturer shall be in line or more stringent than official pharmacopoeias (BP and USP).

d) Details of test methods shall include the following items:
i) List of equipment and apparatus;
ii) List of chemical, reagents and media;
iii) Preparation of solutions such as sample, standard, mobile phase, medium etc.;
iv) Setting up of analytical instrumentation;
v) System suitability tests (resolution, percentage of Relative Standard Deviation (%RSD), tailing factor and theoretical plate for High Performance Liquid Chromatography (HPLC) and Gas Chromatography (GC) methods);
vi) Complete formula for calculation and interpretation of results;
vii) Specification or acceptance criteria.

e) Photocopies or methods directly copied from pharmacopoeias shall not be accepted. In cases where test methods are adopted from official pharmacopeia, details of specific requirements should be submitted.

f) All relevant data collected during chemical and microbiological testing such as chromatograms HPLC/ GC, test reports and formulae used for calculating should also be submitted.

g) All documents should be arranged and labeled accordingly.

2. SPECIFIC REQUIREMENTS

The specific requirements for test methods are based on type of tests and dosage forms of product as stated below:

Categories	Type of Tests	Specific Requirements
Physical & Performance Tests	Physical test (friability, uniformity of weight, pH, etc.)	Specific method for the intended analysis
	Disintegration test	Specific method for related dosage forms
	Dissolution test	a. Dissolution parameters should include: i) type of apparatus ii) type and volume of dissolution medium iii) rotation rate iv) temperature of solution v) sampling time b. Complete formula for calculation especially for extended and delayed release products. c. Method of analysis for example HPLC, UV, etc.

Categories	Type of Tests	Specific Requirements
Quality Test	Identification test such as color test, Fourier Transform Infrared (FTIR), Thin Layer Chromatography (TLC) etc.	Specific method for the intended analysis
	Impurities/ degradation/ purity test	a. Analysis method should include:- i) Placebo solution (if any) ii) Relative retention times of impurities or degradation product b. Complete formula for calculation c. Method of analysis for example HPLC, TLC, etc.
	Assay and uniformity of content	Specific method for the intended analysis
	Biological Assay of Antibiotics	a. Procedure for preparation of following solutions/ substances:- i) Culture medium ii) Buffer solutions iii) Diluents iv) Microorganisms used in assay b. Detailed test method (diffusion or turbidimetric method), which includes: i) Preparation of standard solutions (including steps to counteract the antimicrobial properties of any preservatives, etc. present in the sample) ii) Preparation of test solutions (including any steps to neutralize the antimicrobial properties of any preservatives, etc. present in the sample) iii) Test for Media Sterility and

Categories	Type of Tests	Specific Requirements
		Growth Promotion Test iv) Dilution schemes for test and standard solutions. • Application of test & standard solutions (volume, use of latin squares, etc.) • Incubation temperature & time • Interpretation of result • Detailed calculation for the test including ANOVA table and other data showing validity of test results.
Safety tests	Bacterial Endotoxins Test (BET) or Limulus Amebocyte Lysate (LAL) Test	a. Certificate of analysis for endotoxin and LAL (limulus amebocyte lysate) reagent b. List of depyrogenated or pyrogen-free apparatus, glassware and reagent c. Detailed preparation of standard solutions, LAL reagent/ substrate, sample d. Detailed calculation for determination of maximum valid dilution (MVD) e. The product's endotoxin limit concentration (ELC) and source of information f. Detailed calculation for determination of endotoxin limit concentration if the ELC is not in BP, USP, JP or EP g. Detailed test procedure h. Calculation and interpretation of test result
	Sterility Test	a. List of media and reagent i) Culture media ii) List of rinsing solution, buffer solution and diluent

Categories	Type of Tests	Specific Requirements
		iii) Neutralizing agent (if any) b. Preparation of media & Composition of Rinsing Buffer c. Preparation of test sample (including steps to eliminate antimicrobial activity due to antibiotic samples or samples which contain preservatives). d. Detailed test procedure for sterility test i) Quantity of sample/ Volume of sample ii) Membrane filtration/ Direct inoculation iii) Open System or Closed System (if uses Membrane filtration method) iv) Volume of rinsing fluid v) Volume of media used vi) Incubation time and temperature

Categories	Type of Tests	Specific Requirements
	Microbial Contamination Test	Required for ALL non-sterile products a. Preparation of test sample (including neutralizing of preservatives for samples that contain preservatives) b. Total Viable Aerobic Count • Detailed test procedure for Total Aerobic Microbial Count (TAMC) and Total Yeasts and Molds Count (TYMC) by Plate Count, Membrane Filtration or Most-Probable Number (MPN) method. c. Test for Specified Microorganisms • Detailed test procedure for each specific microorganism tested (including identification and confirmation test) • Specification and acceptance criteria For details, please refer to: *Bil. (4) dlm. BPFK/PKK/12/05*. *Maklumat Lanjutan Tentang Spesifikasi Baru Untuk Ujian Kontaminasi Mikrobial* (30 March 2010)
	Quality Testing for Specific Ingredient	For a product containing specific ingredient such as Aphanizomenon flos aquae, Red Yeast Rice (Monascus purpureus), ingredient(s) derived from seafood and placenta, please refer to **Appendix 6** and **Appendix 7** for the testing requirement(s).

Note:

1. Finished product testing shall be conducted on every batch produced as per approved finished product specifications.
2. Manufacturer shall ensure that products manufactured locally or overseas are free from any contamination of *Burkholderia cepacia*. Please refer to this circular for details:
   Bil. (90) dlm.BPFK/PPP/01/03/ Jld. 2
   Ujian Kontaminasi Burkholderia cepacia (19 December 2012)
3. Products are not allowed to send for gamma radiation treatment for the control of microbial contamination. Please refer to this circular for details:
   Bil. (54) dlm.BPFK/02/5/1.3.
   Aktiviti Pendedahan Produk Berdaftar kepada Sinar Gamma (18 April 2006)

APPENDIX 26

GUIDELINE FOR THE SUBMISSION OF ANALYTICAL METHOD VALIDATION (AMV) DOCUMENTS

1. TYPES OF ANALYTICAL PROCEDURES TO BE VALIDATED

a) Identification tests

b) Quantitative tests for impurities' content

c) Limit tests for control of impurities

d) Quantitative tests of the active ingredient in the sample (assay and dissolution)

e) Bacterial endotoxin test

f) Sterility test

g) Microbial Contamination Test

h) Biological Assay of Antibiotics

*For detailed information on requirements for analytical method validation, please refer to:

1. Checklist for AMV Identification, Assay, Dissolution and Related Substances
2. Checklist for Microbial Contamination Test
3. Checklist for Sterility Test
4. Checklist for Bacterial Endotoxin Test

2. TYPICAL VALIDATION PARAMETERS FOR IDENTIFICATION, ASSAY, DISSOLUTION & RELATED SUBSTANCES TESTS

2.1 FULL VALIDATION FOR IN-HOUSE METHODS

Please refer to **Table I** on the next page.

TABLE I:

Characteristics	Type of Analytical Method			
	Identification	Testing for Impurities		Assay: - dissolution (measurement only) - content/ potency
		Quantitation	Limit	
Accuracy		√		√
Precision **Repeatability** **Interm. Precision**		√ √ (1)		√ √ (1)
Specificity (2)	√	√	√	√
Detection Limit		(3)	√	
Quantitation Limit		√		
Linearity		√		√
Range		√		√

2.2 PARTIAL VALIDATION FOR COMPENDIAL/ PHARMACOPOEIAL METHODS AND SECOND SOURCE

TABLE II:

Characteristics	Type of Analytical Method			
	Identification	Testing for Impurities		Assay: - dissolution (measurement only) - content/ potency
		Quantitation	Limit	
Precision **Intermediate Precision**		√ (1)		√ (1)
Specificity (2)	√	√	√	√
Detection Limit		(3)	√	
Quantitation Limit		√		

Note:

√ signifies that this characteristic is normally evaluated.

(1) In cases where reproducibility has been performed, intermediate precision is not needed.

(2) Lack of specificity of one analytical procedure could be compensated by other supporting analytical procedure(s).

(3) May be needed in some cases.

3. TYPICAL VALIDATION CHARACTERISTICS FOR MICROBIOLOGICAL TESTS:

TABLE III:

Microbiological tests	Validation characteristics
Bacterial Endotoxin Test	a. Test for Confirmation of Labelled Lysate Sensitivity (Verification of criteria for standard curve) b. Test for Interfering Factors (Inhibition/ Enhancement tests)
Sterility Test	Validation (Bacteriostasis or Fungistasis) Test
Microbial Contamination Test	a. Validation of total viable aerobic count (suitability of the counting method in the presence of product) b. Validation of test for specified microorganisms (suitability of the test method)

Note:

1. All the analytical validation done by the industry should be in accordance to ASEAN Guidelines for Analytical Procedures, ICH Technical Requirements for Registration of Pharmaceuticals for Human Use under Validation of Analytical Procedures: Text and Methodology Q2 (R1), British Pharmacopoeia (BP), United States Pharmacopoeia (USP), or Japanese Pharmacopoeia (JP).
2. The applicants should ensure all documents available in the online Quest system are of the latest versions. All correspondence on the protocol of analysis and analytical method validation should comply with any relevant circulars regarding the registration process. Failure to do so may cause cancellation or rejection of product registration.
3. Raw data is required for new product application that is not registered with DCA reference countries.

APPENDIX 27

INSPECTION

The related GMP and GDP guidelines referred are:

Guidelines	Product Type/ Category
PIC/S Guide to Good Manufacturing Practice for Medicinal Products * ** Refer to the Pharmaceutical Inspection Co-operation Scheme (PIC/S) website (www.picscheme.org)*	• Pharmaceuticals (Poison and Non-Poison) • Veterinary Medicinal Products • Investigational Medicinal Products • Active Pharmaceutical Ingredients
GMP Guideline for Traditional Medicines and Health Supplements, 1st Edition, 2008	• Traditional Products • Health Supplements
Guidelines on Good Manufacturing Practice (GMP) for Cosmetics (Annex 1, Part 10)	• Cosmetics
Guideline on Good Manufacturing Practice (GMP) for Veterinary Premixes, 1st Edition, January 2015	• Veterinary Products (Premixes)
Guidelines on Good Distribution Practice (GDP); 3rd Edition 2018 Supplementary Notes on Annex 1: Management of Time and Temperature Sensitive Products (TTSP) of Guideline on Good Distribution Practice	• For activities related to the storage and distribution of products/ cosmetics by manufacturers, importers and wholesalers (where applicable)

Refer to the NPRA website for the latest directives and circulars pertaining to GMP and GDP.

1. FOREIGN GMP INSPECTION

The PRH must provide acceptable evidence to prove that the manufacturer of the product follows an internationally accepted standard of GMP and recognized by the Authority in Malaysia.

The CDCR 1984 requires that the standard of manufacturing and quality control of medicinal products manufactured outside Malaysia be taken into consideration before the products are registered with the Authority. NPRA, as the secretariat to the DCA, is responsible for ensuring that all manufacturers of registered products in Malaysia provide acceptable evidence that the manufacturing premises conform to current GMP requirements. Hence, foreign manufacturers are also subjected to GMP conformity assessments through acceptable GMP evidence or GMP inspection.

For further details and forms, refer to the **Guidance Document Foreign GMP Inspection.**

2. MANAGING CHANGES OF MANUFACTURERS FACILITY

This section only focuses on changes related to manufacturing premises including quality control laboratories and storage/ warehouse facilities. For changes to product particulars, refer to Section E of Post Registration Process, which discusses Amendments to Particulars of a Registered Product.

Changes at the manufacturers' facility can potentially have a quality and safety impact. It is the responsibility of the site to assess information on the changes via a formal change control system and risk management, where applicable. Manufacturers, Importers and Wholesalers are recommended to have a system for categorizing types of changes. All changes to the facility shall be notified to the Centre of Compliance & Quality Control (PKKK) and/ or Centre of Regulatory Coordination & Strategic Planning (PKPSR).

Notification of changes will be reviewed to assess its significance and may be verified during the scheduled GMP inspection. PKKK will communicate further and arrange for an investigative/ for-cause inspection focusing on these changes, if deemed necessary.

Additional Information:

1. This section is applicable to local manufacturers only. For changes of importer or wholesaler particulars, refer to **Section E: Post-Registration Process**

2. For further details, refer to **Table A. Example of Immediate Notification** and **Table B. Example of Periodical Notification.**

Types of notification are immediate and periodical notification:

2.1 Immediate notification

This notification is applicable to manufacturers who plan/ undergo a major/ significant/ substantial change that could have an impact on the product quality and safety. Immediate Notification shall be made to and approved by the Centre of Compliance & Quality Control (PKKK) prior to its implementation.

Immediate Notification shall be submitted as follows:

a) Complete 'Borang Permohonan Penilaian Pelan Susun Atur Premis Pengilang' (BPFK-503) for changes related to manufacturing layout and process flow

OR

b) Official letter, which may include information (at the very least) such as;
   - Description of changes to the facility
   - Plan of changes (E.g. Gantt Chart, Validation Master Plan, etc.)
   - Details of the products affected, where applicable.

Examples of changes are listed in **Table A. Example of Immediate Notification**

2.2 Periodical Notification

This notification is applicable to manufacturers that plan/ undergo a minor change that would not give any impact to the product quality and safety. Periodical Notification can be submitted in the form of official letter, which may include information (at the very least) such as;

- Description of changes
- Plan of changes (E.g. Gantt Chart, Validation Master Plan, etc.)

Examples of changes that require Periodical Notification are as per **Table B. Example of Periodical Notification**

*Note: Both **Table A. Example of Immediate Notification** and **Table B. Example of Periodical Notification** are examples for both regulator and the industry. Requirement for further action is still subject to the evaluation by PKKK based on the risk of the changes proposed/ implemented by the manufacturer.*

Table A. Examples of Immediate Notification

Items	Example	Description	Requirement of BPFK-503	Type of Application under BPFK-503	Documentation Required	Remarks (if any)
1.	Change of Manufacturing site (including drug substance if any)	Require submission of new layout plan E.g. New lot	YES	New premises layout (Processing Fee= RM1000.00)	As per BPFK-503 requirement	Verification of information via GMP inspection, if necessary. Please refer further to Section E.
2.	Introduction of new line/ upgrading clean room	a. Addition of new manufacturing/ packaging line	YES	Revision of existing premises layout (Processing fee: RM 500.00)	As per BPFK-503 requirement	Verification of information via GMP inspection, if necessary. Please refer further to Section E.

Items	Example	Description	Requirement of BPFK-503	Type of Application under BPFK-503	Documentation Required	Remarks (if any)
		b. New Production Block	YES	Revision of existing premises layout (no changes of premises address) (Processing fee: RM 500.00)	As per BPFK-503 requirement	Verification of information via GMP inspection, if necessary. Please refer further to Section E.
		c. Upgrading to clean room E.g. Renovation of the production floor according to clean room requirement	YES	Revision of existing premises layout (Processing fee: RM 500.00)	As per BPFK-503 requirement	Verification of information via GMP inspection, if necessary.

Items	Example	Description	Requirement of BPFK-503	Type of Application under BPFK-503	Documentation Required	Remarks (if any)
3.	Change of Manufacturing/ Packaging Rooms (including manufacturing/ packaging room located in warehouse facility e.g. Centralized dispensing room in warehouse)	a. Relocate or add manufacturing rooms, which affect the process flow	YES	Revision of existing premises layout (Processing fee: RM 500.00)	As per BPFK-503 requirement	Verification of information via GMP inspection, if necessary.
		b. Change of room function	YES	Revision of existing premises layout (Processing fee: RM 500.00)	As per BPFK-503 requirement	
		c. Resizing of the room (without affecting existing process flow)	NO	Not applicable	Notification to PKKK, NPRA	
4.	Change of equipment, or manufacturing process or	Addition of critical equipment	NO	Not applicable	Notification to PKKK, NPRA	Verification of

Items	Example	Description	Requirement of BPFK-503	Type of Application under BPFK-503	Documentation Required	Remarks (if any)
	utility					information via GMP inspection, if necessary.
		Changes/ addition of critical steps in manufacturing (including packaging) process	NO	Not applicable	Notification to PKKK, NPRA	Verification of information via GMP inspection, if necessary. May involve product variation (Refer to CPCE, NPRA)
		Changes/ addition of critical utility, such as water system, pharmaceutical gases and HVAC, etc	NO	Not applicable	Notification to PKKK, NPRA	Verification of information via GMP inspection, if necessary.

Table B. Examples of Periodical Notification

Items	Example	Description	Requirement of BPFK-503	Type of Application under BPFK-503	Documentation Required	Remarks (if any)
1.	Change or addition of warehouse facility	Renovation or addition of new warehouse or alternative warehouse	NO	Not applicable	Notification to PKKK & PKPSR, NPRA	Verification of information via GMP inspection, if necessary. The new warehouse needs to be licensed by NPRA before commencing operation. New Manufacturer's License application is required
2.	Change or addition of QC facility	Renovation or addition of QC facility E.g. Retention sample store, microbiological laboratory, stability chamber etc.	NO	Not applicable	Notification to PKKK, NPRA	Verification of information via GMP inspection, if necessary.
3.	Other renovation (without affecting existing manufacturing layout)	Other renovation E.g. Change of flooring, ceiling, door and wall.	NO	Not applicable	Notification to PKKK, NPRA	Verification of information via GMP inspection, if necessary.

Items	Example	Description	Requirement of BPFK-503	Type of Application under BPFK-503	Documentation Required	Remarks (if any)
4.	Change of key personnel	Applicable to QA/QC Manager, Head of production, Production Pharmacist	NO	Not applicable	Notification to PKKK & PKPSR, NPRA	May involved change of holder of Manufacturer's License.
5.	Addition or replacement of manufacturing equipment, without affecting existing manufacturing layout	a. Replacement of old equipment with new equipment in existing designated room E.g. Replace the old tableting machine with new tableting machine in existing tableting room.	NO	Not applicable	Notification to PKKK, NPRA	Verification of information via GMP inspection, if necessary.

Items	Example	Description	Requirement of BPFK-503	Type of Application under BPFK-503	Documentation Required	Remarks (if any)
		b. Installation of new equipment in existing room E.g. New encapsulation or tableting machine in the existing room.	NO	Not applicable	Notification to PKKK, NPRA	Verification of information via GMP inspection, if necessary.
6.	Change of manufacturer address with no changes in manufacturing site	Changes of building number, postal code, street name, etc.	NO	Not applicable	Notification to PKKK, NPRA Business License from local authority	New Manufacturer's License application is required Please refer to Section E. May involve variation application to update the company details.

Items	Example	Description	Requirement of BPFK-503	Type of Application under BPFK-503	Documentation Required	Remarks (if any)
7.	Change of manufacturer name	Company SSM registration number remain unchanged. No changes on manufacturing facility	NO	Not Appplicable	Notification to PKKK, NPRA SSM Certificate	New Manufacturer's License application is required Please refer to Section E. May involve variation application to update the company details.
8.	Change of manufacturer SSM registration number.	No changes in manufacturing facility	NO	Not applicable	Notification to PKKK, NPRA SSM Certificate	Pre-licensing GMP inspection Please refer to Section E. May involve variation application to update the company details.

Items	Example	Description	Requirement of BPFK-503	Type of Application under BPFK-503	Documentation Required	Remarks (if any)
9.	Cessation of manufacturing operation	Example: • Relocation to new site. • Cessation of business activity	NO	Not Applicable	Notification to PKKK, NPRA Manufacturer's License to be returned to NPRA	Verification of information by PKKK if necessary.

APPENDIX 28

LICENSING

1. TYPES OF LICENSES

Type of Licenses	Activity
Manufacturer's License	Licensee is authorized to manufacture the registered products in the premises specified in the license and to sell by wholesale or supply the products
Import License	Licensee is authorized to import and sell by wholesale or supply the registered products from the address of the premises specified in the license.
Wholesaler's License	Licensee is authorized to sell by wholesale or supply the registered products from the address of the business premises specified in the license

2. LICENSE APPLICATION FORM

The license application for registered products (Manufacturer's License, Import License and Wholesaler's License) shall be submitted via the QUEST system.

Applications must be submitted with the following supporting documents:

a) A copy of Company/ Business Registration Certificate
b) A copy of Business License (Local Authority) for business premises or store (if any)
c) A copy of the Applicant's/ License Holder's Identity Card
d) A copy of the License Holder's Type A License (This document is necessary if products manufactured/ imported/ wholesaled are Scheduled Poison A products or any other products that require a Pharmacist)
e) A copy of previous license (For renewal application only)

An application shall only be processed if it is complete and payment has been approved.

The processing fee shall not be refundable. The processing fee of an application for a Manufacturer's License is RM 1,000.00 and RM 500.00 for an Import License or a Wholesaler's License.

Each license is valid for **one (1) year** or until 31 December, whichever earlier.

3. ADDITIONAL PRODUCT LIST OF LICENSES FOR REGISTERED PRODUCTS

Application of Additional Product List of a License is required when there is:

a) Additional newly registered/ renewed products,
b) Change in product registration details (E.g. Product name, product manufacturer, etc.), or
c) Omission of registered products from the product list issued together with the Manufacturer's License or Import License.

When submitting the application for Additional Product List of License for Registered Products, a copy of the current Manufacturer's License/ Import License and a copy of approval letter from the Authority (The Authority's meeting result) shall be provided as supporting documents.

The application of additional list shall be submitted via the QUEST system.

APPENDIX 29

CERTIFICATE

1. CERTIFICATE OF PHARMACEUTICAL PRODUCT (CPP)

A CPP in the format recommended by WHO for a registered product can be applied by the PRH where such certificate is required by any country importing such product.

To apply a CPP, the PRH shall fill up completely and submit the online application form via the QUEST system.

A fee, as stated in **Appendix 9: Fees**, is payable on the issue of such certification.

Upon receipt of complete application, the certificate shall be issued within fifteen (15) working days.

For imported products, the following requirements shall be furnished, either a:

i) CPP from the competent authority in the country of origin; OR
*(**Note:** In the event a CPP is not available from the country manufacture, e.g. where a product is not licensed for sale in said country because its manufacturer is manufacturing under contract only for product owner from another country, the following alternatives may be considered: GMP Certification/ Manufacturing License for the manufacturer from the relevant competent authority, together with CPP from the country of the product owner; or CPP from country of release, if CPP from the country of the product owner is not available)*

ii) CFS and GMP from the relevant competent authorities is deemed acceptable by the Authority for health supplements and natural products only.

CPP shall be in the format of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce & be issued by the Health Authorities listed in the WHO Certification Scheme (*list is available from WHO website*: *http://www.who.int*).

CPP which is issued by EMA for products registered through the centralized procedure in EU will be accepted.

CPP issued by the manufacturer or other authorities are not acceptable.

If more than one manufacturer is involved in the manufacture of a product, GMP certification shall be available for all the manufacturers.

The Authority reserves the right to conduct an inspection on any manufacturing site.

Unless otherwise supported by justifications acceptable to the Authority, the following products are unlikely to be registered:

i) products not licensed/ certified for sale in the country of manufacture/ product owner;
ii) products manufactured for export only (imported products).

2. GOOD MANUFACTURING PRACTICE (GMP) CERTIFICATE

According to the CDCR 1984, compliance to Good Manufacturing Practice (GMP) is a prerequisite to the application of a Manufacturer's license, as well as product registration/ cosmetic notification.

GMP is a standard which shall be followed by the manufacturers to ensure that the products manufactured are safe, efficacious and of quality.

A GMP Certificate is issued for the purpose of exporting locally manufactured registered products. It endorses that the local manufacturer complies with the current GMP requirements. These certificates are required by overseas regulatory agencies for the purpose of product registration in their respective countries. Thus, when filling in the GMP Certificate application form, it is crucial for the company to provide the correct address of the overseas regulatory agency.

Upon complete application, a GMP certificate will be issued. A fee of RM50.00 is payable for the issuance of such certification.

The application of GMP Certificate by local manufacturers shall be submitted via the online QUEST system, while applications from foreign manufacturers that have been inspected by NPRA shall be submitted manually via *Borang BPFK-420 Permohonan Sijil Amalan Perkilangan Baik (APB) Pengilang Luar Negara.*

APPENDIX 30

CONDITIONS AND SUPPORTING DOCUMENTS REQUIRED FOR AN APPLICATION OF VARIATION

a) VARIATION TYPE I (MINOR VARIATION)

NO.	VARIATION TYPE I (MINOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
1.	Change in name of manufacturer and/or other manufacturers without any change in address of site.	• E13 (manufacturer) • E14 (other manufacturers) • D1 • D2 • D3 • E6 • E12	• E2 (manufacturer) • E3 (other manufacturers) • D1 • D2 • D3 • F6 • F12	<u>CONDITIONS</u> 1. The manufacturing/ other manufacturing site of the drug product remains unchanged. 2. No other changes to the label/ package insert except for the change of the name of a manufacturer/ other manufacturers of the drug product. 3. The manufacturing site remains the same. <u>SUPPORTING DOCUMENTS</u> 1. For local manufacturers/ other manufacturers: Certificate of name change i.e. Form 13 Company Act 1965. (Please attach the supporting document at E12/ F12).

NO.	VARIATION TYPE I (MINOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
				2. For foreign manufacturers/ other manufacturers: A valid Good Manufacturing Practice (GMP) certificate. 3. Official letter from product owner authorizing the manufacturer with new name to manufacture the drug product. 4. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).
2.	Replacement, addition or deletion of company logo on the packaging components (without any changes on graphic or label content)	• D1 • D2 • D3	• D1 • D2 • D3	<u>SUPPORTING DOCUMENT</u> Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).

NO.	VARIATION TYPE I (MINOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
3.	Change in product owner	• E1.1 • E1.2 • E2.1 • E2.2 • E12 • D1 • D2 • D3 (if applicable)	• E1 • F1 • F2.1 • F2.2 • F12 • D1 • D2 • D3 (if applicable)	<u>CONDITIONS</u> 1. The Product Registration Holder remains the same. Submission shall be done by current PRH. 2. The manufacturing site remains the same. <u>SUPPORTING DOCUMENTS</u> 1. Letter of confirmation for change in product ownership countersigned by both old and new product owner. 2. Official letter from the new product owner declaring the change, and authorizing the local license holder to be responsible for the product license. 3. In the case of a contract manufacturer, new product owner to issue Letter Of Appointment to contract manufacturer and contract manufacturer to issue Letter Of Acceptance. 4. Revised labels and package insert (if applicable).
4.	Change in importer/ store address.	• E13.1 (importer) • E15 (store address)	• E2.1 (importer) • E4 (store address)	

NO.	VARIATION TYPE I (MINOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
5.	Change or addition of imprints, bossing or other markings (except scoring/break lines) on tablets or printing on capsules, including replacement, or addition of inks used for product marking.	• A4 • P1 • P5.1 • P5.2 • D3 • E8 (if applicable) • E9	• A2 • D3 • F8 (if applicable) • B4 • F9	<u>CONDITIONS</u> 1. Any new ink must be of oral pharmaceutical/ food grade and not a listed banned substance. 2. Release and end-of-shelf life specifications of the drug product remain unchanged except for appearance. 3. New markings do not cause confusion with other registered products. <u>SUPPORTING DOCUMENTS</u> 1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Release and end-of-shelf life specifications of the drug product with the new product description. 3. Certificate of analysis (CoA) of new ink. 4. Details of the proposed new inks (where applicable) 5. Detailed drawing or written description of the current and proposed imprint/ bossing/ markings.

NO.	VARIATION TYPE I (MINOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
6.	Change in shape or dimensions of the container or closure without any other changes.	• P7 • C (if applicable)	• C (if applicable)	CONDITIONS 1. The primary packaging material of container or closure remains the same. 2. Not applicable for sterile products. 3. No change is made to the product shelf life and/or storage conditions. 4. No change in the qualitative or quantitative composition of the container and/or closure and the change do not affect the delivery, use, safety or stability of the drug product. SUPPORTING DOCUMENTS Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).
7.	• Change in pack size of the drug product (Finished product), without change in primary packaging material. (including pack size meant as samples) • Change in the number	• C • D1 • D2 • D3 • E8 (if applicable) • P7	• C • D1 • D2 • D3 • F8 (if applicable)	CONDITIONS 1. The primary packaging material of container or closure remains the same. Primary packaging material is the material that is in contact with the finished product and may affect the delivery, use, safety or stability. 2. No other changes to the label/ package insert except for the pack size. 3. The new size is consistent with the dosage regimen and duration of use as approved in the package insert.

NO.	VARIATION TYPE I (MINOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
	or units (e.g. tablets, ampoules) in a pack. • Change in volume of non sterile preparations			*The sentence 'Sample not for sale' can be added in the product label without going through variation approval. <u>SUPPORTING DOCUMENTS</u> Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).
8.	Tightening of specification limits of drug product (finished product) and/or drug substance (active ingredient)	• E9 • E10 • E11 • P5.1 • P5.2 • P5.4 • S4.1 • S4.2 • S 4.4	• B4 • F9 • F10 (finished product) • F11 (active ingredient)	<u>CONDITION</u> 1. Any change should be within the range of currently approved limits. <u>SUPPORTING DOCUMENTS</u> 1. Tabulation of the current and revised release and shelf life specifications of the drug product/drug substance with changes highlighted. 2. Certificate of Analysis (CoA) for drug product or drug substance. 3. Protocol analysis for drug product/ drug substance. 4. Revised specification of drug substance. 5. Specifications of drug product. 6. Batch analysis of drug product.

NO.	VARIATION TYPE I (MINOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
9.	Change in particular of manufacturer of drug substance (active ingredient) without any change in specification a. Change in manufacturer of drug substance b. Addition of manufacturer of drug substance c. Change in name and/or rephrasing of address of a manufacturer of drug substance.	• S2.1 • S4.4	• F11	<u>CONDITIONS</u> 1. Finished product release and end of shelf life specification remains the same. 2. Method of preparation and route of synthesis remain the same. 3. For (c), the manufacturing site of the drug substance remains the same. <u>SUPPORTING DOCUMENTS</u> **For (a) & (b):** 1. Certificate of Analysis (CoA) for drug substance (Also include CoA from all of the drug substance manufacturers proposed to be retained) or batch analysis of drug substance. 2. Certificate of Suitability (CEP) for the drug substance or Drug Master File; or reference to DMF by USFDA, TGA or JFDA (if applicable). 3. Tabulation of the differences compared with the registered manufacture information (if applicable). **For (c)**: 1. Updated information of the manufacturer of the drug substance. 2. Official document/ evidence when required.

NO.	VARIATION TYPE I (MINOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
10.	Change in secondary packaging material (or change in any part of the primary packaging material that is not in contact with the finished product (e.g. colour of flip off caps, colour code rings on ampoules, change of needle shields i.e. different plastic used).	• C • D2 • D3 • P7	• C • D2 • D3	<u>CONDITIONS</u> 1. The primary packaging material of container or closure remains the same. 2. The change does not affect the delivery, use, safety or stability of the finished product <u>SUPPORTING DOCUMENT</u> Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).
11.	Change in testing procedure of an excipient	• P4.2 • P4.3	Not applicable	<u>CONDITION</u> Specifications of the excipient and drug product (finished product) remain the same.

b) VARIATION TYPE II (MAJOR VARIATION)

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
1.	Change of product name.	• A1 • D1 • D2 • D3 • E4 (if applicable) • E8 (if applicable)	• A1 • D1 • D2 • D3 (if applicable) • F4 (if applicable) • F8 (if applicable)	CONDITIONS 1. No change to product (formulation, specification etc) except for the product name 2. No confusion with other already registered product's name. 3. The new name does not (1) suggest greater safety or efficacy than supported by clinical data (2) imply a therapeutic use (3) imply superiority over another similar product (4) imply the presence of substance(s) not present in the product. 4. Health Supplements & Natural Products - Please refer to **Appendix 6** and **Appendix 7**, respectively. SUPPORTING DOCUMENTS 1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Letter confirming change in name only issued by the product owner or PRH. 3. A declaration from the applicant that there is no change to the product/ label except name. 4. Updated CPP if applicable.

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
2.	Change in content of leaflet or prescribing information/ PIL/ SPC.	• A1 – A17 • D1 • D2 • D3 • E7 • E8 (if applicable)	• A1 – A13 • D1 • D2 • D3 • F7 • F8 • F12	<u>CONDITION</u> As a subsequent change due to revision of datasheet approved by regulatory authority e.g. Summary of Product Characteristics (SPC), or US Package Insert (USPI) or equivalent document. For natural products: Proposed indication shall be within those listed under **Appendix 7**. <u>SUPPORTING DOCUMENTS</u> 1. For all types of product please provide revised drafts of the package insert and labeling incorporating the proposed variation with: a. Copy with amendments clearly marked. b. Clean copy of the proposed new package insert. 2. For innovator product please provide: a. Datasheet approved by regulatory authority e.g. Summary of Product Characteristics (SPC), or US Package Insert (USPI) or equivalent document. b. Conclusion or abstract of recent Periodic Safety Update Report where applicable. c. Expert Clinical Report (if applicable) d. Company Core Datasheet where applicable.

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
				3. For generic product please provide supporting documents e.g. Martindale or equivalent document to support the change. 4. For natural products, please provide: a) Justification for the proposed change. b) Supporting documents from the clinical papers, Chinese Pharmacopoeia and/or herbal monograph/ compendium on the therapeutic uses and safety aspect of the relevant active ingredient/s.
3.	Change in content of label inclusive of change in graphics/ artwork.	• D1 • D2 • D3	• D1 • D2 • D3	<u>CONDITIONS</u> For Natural Products, please refer to: List of Prohibited Visuals/ Graphics On Label of Natural Products in **Appendix 7** <u>SUPPORTING DOCUMENT</u> Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
4.	Change in manufacturing process of the finished product	• E11 • P3.2 • P3.2.1 • P3.3 • P3.4 • P5.1 • P5.4 • P8	• B2.1 • B2.2 • B3 • B4 • B5 • F10 (CoA of finished product)	<u>CONDITIONS</u> 1. The same currently approved manufacturing site. 2. The change does not cause a negative impact on the quality, safety and efficacy of the drug product. 3. Finished product specification is not adversely affected. <u>SUPPORTING DOCUMENTS</u> 1. Description of the proposed change in manufacturing process. 2. Comparative batch analysis data between the currently approved and proposed manufacturing processes OR Certificate of Analysis (CoA), where applicable. 3. Stability data of drug product (please refer to ASEAN Guideline on Stability Study of Drug Product) where applicable. 4. Comparative dissolution profile data between the products manufactured in the currently approved and proposed manufacturing process for oral solid dosage forms as per compendium and validation batches, where applicable. 5. Justification for not submitting a new bioequivalence study according to ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies, where applicable.

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
				For abridged-products, only supporting documents (1), (2) and (3) are required. Process validation report may be requested when deemed necessary.
5.	Change in overage of active ingredient	• B1.2 • E11 • P5.4 • E12 • P8	• B1.2 • F10 • F12 • B5	<u>CONDITION</u> Finished product release and end of shelf life specification remains the same. <u>SUPPORTING DOCUMENTS</u> 1. Certificate of Analysis (CoA) of drug product. 2. Justification for the change. 3. Stability data of drug product (please refer to ASEAN Guideline on Stability Study of Drug Product) where applicable. 4. Batch manufacturing formula. 5. Comparative batch analysis data of drug product. 6. Table of comparison of proposed and current batch manufacturing formula. 7. Letter of commitment to undertake the proposed change under real time stability study.

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
6.	Replacement of an excipient with a comparable excipient and/or change in content of excipient.	• A2.1 • B1.2 • P1 • P4.1 • P4.2 • P3.2 • P3.2.1 • E11 • P5.4 • P8 • E12 • D1 • D2 • D3 (if applicable)	• A4.2 • B1.2 • B2.1 • B2.2 • B3 • B4 • B5 • F10 • F12 • D1 • D2 • D3 (if applicable)	<u>CONDITIONS</u> 1. Finished product release and end of shelf life specification remains the same. 2. There is no change in dissolution profile for oral solid dosage forms (where applicable). 3. Replacement of an excipient with a comparable excipient of the same functional characteristics. 4. No changes on the specification of the excipient for product specific requirements (e.g. particle size profiles, polymorphic form, etc.), if applicable. 5. Any new excipient does not include the use of materials of human or animal origin for which assessment is required of viral safety data. <u>SUPPORTING DOCUMENTS</u> 1. Comparison of new and existing formula. 2. Batch Manufacturing Formula. 3. Excipient specification (if applicable). 4. Manufacturing process with amendments. 5. Certificate of Analysis (CoA) of drug product. 6. Justification for not submitting a new bioequivalence study according to ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies (where applicable). 7. Comparative dissolution profile data of at least one representative pilot/production batch of the drug product

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
				between the currently approved and proposed solid dosage forms formulation (where applicable). 8. Stability data of drug product (please refer to ASEAN Guideline On Stability Study of Drug Product) 9. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 10. Batch analysis data. 11. Product interchangeability/ equivalent evidence (if any). 12. Justification for the change supported by appropriate development of pharmaceutics. 13. New unit formula for coating agent (where applicable).
7.	Change in batch size	• B1.2 • E11 • P5.4 • P3.4 • E12 • P3.2 • P3.2.1 (if applicable)	• B1.2 • F10 • F12 • B2.1 • B2.2 (if applicable)	<u>CONDITIONS</u> 1. The change does not affect the reproducibility and/or consistency of the product. 2. No change to the manufacturing method nor to the in-process controls other that those necessitated by the change in batch-size, e.g. use of different size equipment. 3. Finished product release and end of shelf life specification remains the same.

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
				SUPPORTING DOCUMENTS 1. Comparative tabulated format of the proposed and current manufacturing formula. 2. New batch manufacturing formula. 3. Batch analysis data (in a comparative table). 4. Certificate of analysis for 2 batches of drug product. 5. Process validation report (may be requested when deemed necessary). 6. Justification for the change. 7. Letter of commitment to undertake the proposed batch size under real time stability studies. 8. Description of the manufacturing process (if applicable).
8.	Change in hard capsule shell (colour, size or source)	• A4 • P1 • P8 • E11 • P4.5 • P5.4 • E12 • P5.1 • E9 • D1 • D2 • D3 (if applicable)	• A2 • A3.2 • B4 • B5 • F9 • F10 • D1 • D2 • D3 (if applicable)	CONDITIONS 1. Includes change of hard gelatin capsule to vegetable capsule but does not apply change from hard gelatin capsule to soft gel capsule. 2. Any new coloring agent used must be of oral pharmaceutical/ food grade and not a listed banned substance. 3. Same functional characteristics, no change in dissolution profile for solid dosage forms 4. Finished product release and shelf life specifications remain the same except for the product description.

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
				SUPPORTING DOCUMENTS 1. Stability data of drug product (please refer to ASEAN Guideline on Stability Study of Drug Product) where applicable. 2. Certificate of analysis (CoA) of drug product with the new description. 3. For empty hard capsule made of ruminants source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate issued from relevant veterinary authority of the issuing country. 4. Certificate of analysis of the new capsule shell. 5. Revised specifications of drug product. 6. Batch analysis data. 7. Comparative dissolution profile data of drug product. 8. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
9.	Change in finished product or active ingredient specification (includes addition of a new test parameter)	• E9 • E10 • E11 • P5.1 • P5.4 • P5.6 • S4.1 • S4.2 • S4.3 • S4.4	• B4 • F9 • F10 • F11	<u>CONDITIONS</u> The change should not be the result of unexpected events arising during manufacture or because of stability concerns. <u>SUPPORTING DOCUMENTS</u> 1. For change in finished product specifications: a. Certificate of analysis of drug product as per the new specifications: b. Comparative table of approved and proposed specifications with justification c. Appropriate analytical validation data d. Revised specifications of drug product. e. Revised analytical procedures. f. Batch analysis data of drug product. 2. For change in active ingredient/ drug substance specifications: a. Comparative table of approved and proposed specifications with justification b. Specification of drug substance, c. Analytical procedures of drug substance, d. Validation of analytical procedures, e. Batch analysis of drug substance

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
10.	Change to in-process tests or limits applied during manufacture of the product.	• P3.3 • P3.4 • E9 • E10	• B3 • F9	<u>CONDITIONS</u> 1. Includes tightening of in-process limits and addition of new tests 2. Release and shelf-life specifications of drug product remain unchanged <u>SUPPORTING DOCUMENTS</u> 1. A description of the analytical methodology and summary of validation data must be provided for all new analytical methods (where applicable). 2. Revised in-process specifications together with justification and relevant process validation data.

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
11.	Change or addition in primary packaging material	• C • D1 • D2 • D3 • P3.2 • P3.2.1 • P7 • P8 • E8 (if applicable), • E12	• C • D1 • D2 • D3 (if applicable), • B5, • F8 (if applicable) • F12	<u>CONDITIONS</u> Release and shelf life specification remains the same. <u>SUPPORTING DOCUMENTS</u> 1. Assembly process for the new packaging material/ revised manufacturing process and revised flow chart (if any) 2. Stability data of drug product (please refer to ASEAN Guideline on Stability Study of Drug Product) where applicable. 3. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 4. Justification for the change in packaging material and appropriate scientific studies on the new packaging. 5. For semisolid and liquid dosage forms, proof must be provided that no interaction between the content and the packaging material occurs. (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack). 6. Container closure system (if applicable).

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
12.	Change in shelf life of finished product:- a) As packaged for sale b) After first opening c) After dilution/ reconstitution	• A16 • P8 • E12 • D1 • D2 • D3	• A13 • B5 • F12 • D1 • D2 • D3	<u>CONDITIONS</u> 1. **For (a) & (b)** - The studies must show conformance to the current shelf life specification. 2. **For (c)** - Studies must show conformance to the current shelf life specification for the reconstituted product. <u>SUPPORTING DOCUMENTS</u> 1. Results of appropriate real time stability studies covering the duration of proposed shelf-life of at least 2 pilot/ production scale batches of the product in the authorized packaging material • as a package for sale and/or • after first opening and/or • after the dilution/ reconstitution In accordance with the ASEAN Guidelines on Stability Study of Drug Product; results of appropriate microbiological testing should be included (where appropriate). 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. Justification letter for the change of shelf life of the drug product (if applicable).

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
13.	Change in storage conditions	• A15 • P8 • D1 • D2 • D3	• A12 • B5 • D1 • D2 • D3	<u>CONDITION</u> The studies must show conformance to the current shelf life specification. <u>SUPPORTING DOCUMENTS</u> 1. Results of appropriate real time stability studies covering the duration of currently approved end-of-shelf life (at proposed storage condition) of at least 2 pilot/ production scale batches of the product and in the authorized packaging material in accordance with the ASEAN Guidelines on Stability Study of Drug Product. 2. Revised drafts of the package insert and labeling incorporating the proposed variation (if applicable).
14.	Appointment, deletion or change of other manufacturers	• D1 • D2 • D3 • E14 • E12	• E3 • F12 • D1 • D2 • D3	<u>SUPPORTING DOCUMENTS</u> 1. GMP certificates of the proposed other manufacturers. 2. Description of the manufacturing activity of all other manufacturers involved (including assembling process). 3. Letter of appointment and acceptance for contract of other manufacturers. 4. Revised drafts of the labeling incorporating the proposed variation (where applicable).

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
15.	Addition or deletion of scoring/ break line on tablet	• A4 • P1 • D1 • D2 (if applicable) • D3 • E9 • E11 • P5.1 • P5.4 • E12	• A2 • B4 • F9 • F10 • F12 • D1 • D2 • D3 (if applicable)	<u>CONDITIONS</u> Finished product release and shelf life specifications remain the same except for the product description. <u>SUPPORTING DOCUMENTS</u> 1. Certificate of analysis (CoA) FPQC X 1 batch (shall include data on the test of uniformity of content of the subdivided parts of tablets at release). 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. Release and end-of-shelf life specifications of the drug product with the new product description.
16.	Change in test procedure or analytical protocols of finished product.	• E9 • E10 • E11 • P5.4	• B4 • F9 • F10	<u>CONDITIONS</u> 1. Finished product specifications are not adversely affected. 2. Appropriate analytical validation or re-validation studies have been performed in accordance with relevant guidelines. 3. Results of method validation show new test procedure to be at least equivalent to the former procedure.

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
				<u>SUPPORTING DOCUMENTS</u> 1. Appropriate verification/ validation data and comparative analytical results between the currently approved and proposed test. 2. Revised protocol of analysis. 3. Certificate of analysis of drug product.
17.	Change or addition of fill volume and/or change of shape or dimension of container or closure for a sterile solid and liquid drug product	• P3.4 • P8 • E12 • C • D1 • D2 • D3 (if applicable)	Not applicable	<u>CONDITIONS</u> 1. Release and end-of-shelf life specifications of the drug product are not affected. 2. The packaging material remains the same. <u>SUPPORTING DOCUMENTS</u> 1. Justification that the proposed pack size is consistent with the dosage regimen and duration of use as approved in the package insert. 2. Validation data of the manufacturing process, sterilization and container closure system (if applicable). 3. Stability data of drug product (please refer to ASEAN Guideline on Stability Study of Drug Product) where applicable. 4. Revised drafts of the package insert and labeling incorporating the proposed variation, where applicable.

APPENDIX 31

CHANGE OF MANUFACTURING SITES (COS)

Change of Manufacturing Site (COS) refers to change of manufacturing site for certain or all of the manufacturing process of a product. This does not cover changes related to a new site, where only:

a) batch release takes place OR

b) to a new packager (secondary packaging or labelling), as these changes are covered under applications for amendments to the particulars of a registered product

However, a change of manufacturing site for biologics shall require a new product registration if the change is extensive and will have an impact on the quality, safety and efficacy profile of the final product.

Once NPRA deems the application is complete, the outcome of the COS application shall be decided by the Drug Control Authority (DCA) within sixty (60) working days.

1. CONDITIONS ON APPLICATION FOR COS:

COS is only applicable for the following situations:

a) a change in manufacturing site for the same company, including rationalization in the event of mergers; or

b) a company that previously contracts out the manufacture of its product(s) transfers the manufacture of the product to its own manufacturing premises; or

c) a company appoints a contract manufacturer in Malaysia for pharmaceutical products, i.e. scheduled poison, non-scheduled poison & health supplement products **except** natural products. This change includes a change from a contract manufacturer to a local contract manufacturer or a change from own manufacturing premise to a local contract manufacturer.

   Note: The change in manufacturing site for this condition will not be considered if the change is made without acceptable justification or submitted too frequently.

A change of manufacturing site under a **crisis situation** may be considered for the following:

a) A change between contract manufacturers for local natural and health supplement products;

b) A change to a contract manufacturer outside of Malaysia for pharmaceutical products.

Validity of registration for a product approved for change of manufacturing site remains unchanged.

2. TYPES OF COS

No.	Types of COS		Description
1.	**Type I**	Change of manufacturing site within Malaysia	Change in the location of the site of manufacture within Malaysia only. This change may be due to upgrading of facilities, and/ or expansion of manufacturing activities or moving to a newly constructed plant, or appointment of a contract manufacturer for pharmaceutical products.
2.	**Type II**	Change of manufacturing site from foreign country to Malaysia	Change in location of the site of manufacture from outside of Malaysia to a location in Malaysia. This change may be due to the ability of the local counterpart to manufacture the product, or appointment of a contract manufacturer for pharmaceutical products.
3.	**Type III**	Change of manufacturing site located outside Malaysia	Change of location of the site of manufacture to manufacturing facilities located outside Malaysia. This may be due to a merger or rationalization of manufacturing sites in line with multinationals' manufacturing strategies.

No.	Types of COS		Description
4.	**Type IV**	Change of manufacturing site for sterile products	i) Transfer of manufacturing of an aseptically processed sterile product to a: a) newly constructed or refurbished aseptic processing facility or area; b) an existing processing facility or area that does not manufacture similar approved products. (For example, transferring the manufacture of a lyophilized product to an existing aseptic process area where there is no approved lyophilized product is manufactured). ii) Transfer of a finished product sterilized by terminal processes to a newly constructed facility at a different manufacturing site.
5.	**Type V**	Change of manufacturing site in crisis situation	i) Change of location of the site of manufacture that is deemed necessary due to certain circumstances such as natural disasters, closure or suspension of premise (revocation of manufacturing license), bankruptcy and matters related to breach of product quality, safety and efficacy ONLY. ii) Prior to submission of Type V COS, approval letter issued by the secretariat of the Authority shall be obtained. iii) Application for Type V COS must be made within **six (6) months** from the date of the crisis. iv) Type V COS applications for natural products and health supplements are only applicable for local manufacturers.

3. MODE OF SUBMISSION

Applicant shall submit the application via the QUEST system.

4. SUPPORTING DOCUMENTS REQUIRED FOR COS APPLICATION

4.1 GENERAL REQUIREMENTS FOR ALL CATEGORIES OF PRODUCTS

For the list of documents to be submitted for each type of COS applications, kindly refer to the table below:

No	Document to Be Submitted	Type I *(Except Natural Product)*	Type II	Type III	Type IV	Type V
1.	Letter of authorization/ appointment from the product owner to authorise Product Registration Holder to submit the change of site application. In case of a contract manufacturer, a letter of acceptance from the proposed contract manufacturer to manufacture the product.	√	√	√	√	√
2.	Letter from the manufacturer/ product owner to clarify/ explain the need to change site of manufacture.	√	√	√	√	√
3.	Written declaration from the manufacturer to certify that the manufacturing process, and the release and expiry (check) specifications of the product as the same as already approved. *OR* If there are minor changes, to declare the 'minor changes' & justify the need for such changes.	√	√	√	√	√
4.	'Release' and 'end-of-shelf life' specifications from proposed site.	√	√	√	√	√
5.	Original copy of the Certificate of Free Sale (CFS) / Certificate of Pharmaceutical Product (CPP) and notarised Good Manufacturing Practice (GMP) from the source country of the new manufacturing site in the case of an imported product *OR* Letter of confirmation on GMP status or valid manufacturer's license for the new manufacturing site.	√	√	√	√	√

No	Document to Be Submitted	Type I *(Except Natural Product)*	Type II	Type III	Type IV	Type V
6.	Specification of the drug substance	√	√	√	√	√
7.	Product formula/ Batch Manufacturing Formula	√	√	√	√	√
8.	Original copy of Certificate of Analysis (CoA) from the new manufacturing site.	√	√	√	√	
9.	Comparative batch analysis data of drug product of at least two production batches (or one production batch and two pilot batch) from the proposed site and last three batches from the current site; batch analysis data on the next two full production batches should be available upon request or reported if outside specifications (with proposed action).	√	√	√	√	
10.	"Accelerated" and on-going stability data as per ASEAN Guideline on Stability Study of Drug Product or Health Supplement/ Traditional Medicine and a letter of commitment to submit real time stability data.	√	√	√	√	
11.	Amended immediate label, outer label and package insert for the product from the proposed site.	√	√	√	√	√
12.	Process validation report as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration.	√	√	√	√	
13.	Holding time studies testing of bulk pack during storage and transportation between the bulk production site and primary packager (where applicable).	√	√	√	√	
14.	Letter of commitment to submit stability data, certificate of analysis and process validation report (where applicable) within 6 months of approval of site change.					√

No	Document to Be Submitted	Type I *(Except Natural Product)*	Type II	Type III	Type IV	Type V
15.	A written plan for assessing the effect of the change of site on the quality of the product with the objective of demonstrating that the pre- and post-change products are equivalent.	√	√		√	
16.	Comparative dissolution profile between the proposed and current site for oral solid dosage forms that are entitled for "biowaiver". *For further information, please refer to circular:* *Bil. (31) dlm. BPFK/PPP/01/03* *OR* Report of bioavailability and bioequivalence studies for generic products. *OR* Comparative dissolution profile between the proposed and current site for oral solid dosage forms for innovator products, if applicable. (*Please refer to ASEAN Guidelines and list of products requiring BA and BE study).*	√	√	√		

No	Document to Be Submitted	Type I *(Except Natural Product)*	Type II	Type III	Type IV	Type V
17.	Letter of commitment to submit comparative dissolution profile between the proposed and current site for oral solid dosage forms that are entitled for "biowaiver". *For further information, please refer to circular:* *Bil. (31) dlm. BPFK/PPP/01/03* *OR* Letter of commitment to submit report of bioavailability and bioequivalence studies for generic products. *OR* Letter of commitment to submit comparative dissolution profile between the proposed and current site for oral solid dosage forms for innovator products, if applicable. *(Please refer to ASEAN Guidelines and list of products requiring BA and BE study).*					√

<u>Note:</u>
No. 6, 9, 12, 13, 16 and 17 in the table above are <u>not applicable</u> for Natural Products and Health Supplements.

4.2 Supporting Documents Required for Type I COS Application (Natural Products)

No.	Documents to Be Submitted
1.	Letter of authorization/ appointment from the product owner to authorise Product Registration Holder to submit the change of site application. In case of a contract manufacturer, a letter of acceptance from the proposed contract manufacturer to manufacture the product.
2.	Letter of declaration stating the reason(s) for change of manufacturing site and clearly state the proposed and current name and address of manufacturer
3.	Written declaration from the manufacturer to certify that the manufacturing process, and the release and expiry specifications of the product as the same as already approved. *OR* If there are minor changes, to declare the 'minor changes' & justify the need for such changes.
4.	'Release' and 'end-of-shelf life' specifications from proposed site.
5.	Letter of confirmation on GMP status or valid manufacturer's license for the new manufacturing site.
6.	Product formula/ Batch Manufacturing Formula
7.	Amended immediate label, outer label and package insert for the product from the proposed site.
8.	Declaration and commitment that the manufacturer will carry out continuous quality monitoring on the post change products
9.	Letter of commitment to submit stability data and certificate of analysis after approval of site change.
10.	A written plan for assessing the effect of the change of site on the quality of the product with the objective of demonstrating that the pre- and post-change products are equivalent.

5. OTHER INFORMATION

a) Application for COS will be rejected if the applicant failed to submit required data within **six (6) months** from the first correspondence date;

b) All supporting documents are required to be submitted in accordance to the specified conditions for each type of COS.

c) If deemed necessary, NPRA reserves the right to request for additional supporting documents.

d) For further information, refer to:

i. *Bil. (59) BPFK/17/VF/9.2*
Prosedur Permohonan Pertukaran Tapak Pengilang Produk Berdaftar: Polisi Menolak Permohonan Pertukaran Tapak Pengilang Sekiranya 'Tiada Maklumbalas/ Maklumbalas Tidak Lengkap' Dikemukakan Oleh Pemohon Dalam Tempoh Enam (6) Bulan Dari Tarikh Permintaan (20 May 2009)

ii. *Bil. (22) dlm. BPFK/PPP/01/03*
Keperluan Kajian Bioekuivalens Bagi Produk "Generic Immediate Release Oral Solid Dosage Form" *yang Bertukar Tapak Pengilangan* (1 February 2009)

iii. *Bil. (31) dlm. BPFK/PPP/01/03*
Makluman Susulan Berkaitan Kajian Bioekuivalens Bagi Produk 'Generic Immediate Release Oral Solid Dosage Form' *yang Bertukar Tapak Pengilangan* (13 May 2009)

iv. *Bil. (39) dlm. BPFK/PPP/01/03*
Permohonan Pertukaran Tapak Pengilang Jenis V Iaitu Pada Situasi Krisis (16 July 2009)

v. *Bil. (10) dlm.BPFK/PPP/01/03 Jilid 1*
Directive No. 1, 2011*: Direktif Penguatkuasaan Keperluan Kajian Bioekuivalens Bagi Semua Produk Generik* "Immediate Release, Oral, Solid Dosage Form" *Yang Mengandungi Bahan Aktif Racun Berjadual Serta Akreditasi Pusat Kajian Bioekuivalens* (2 March 2011)

vi. *Bil. (7)dlm.BPFK/PPP/01/03 Jld. 3*
Kebenaran Pertukaran Tapak Pengilang Ke Pengilang Kontrak Tempatan (18 February 2014)

APPENDIX 32

CHANGE OF PRODUCT REGISTRATION HOLDER (COH)

1. INTRODUCTION

Change of PRH (COH) refers to a transfer procedure for the purpose of changing the existing product registration holder (PRH) that is authorized to market a registered product in Malaysia to another holder. This procedure allows the registered product to maintain the same registration number.

Once NPRA deems the application is complete, the outcome of the change of PRH application shall be decided by the Drug Control Authority within **forty-five (45) working days**.

2. CONDITIONS

The application is subjected to the following conditions:

1) An application to transfer the marketing authorization of a registered product shall be submitted by the **existing PRH**.
2) The new PRH shall be a registered company/ business with Companies Commissioner of Malaysia (SSM) and a registered QUEST user with NPRA.
3) The registered product intended for transfer to a new PRH shall have a remaining registration validity **period of at least six (6) months**. If the registration validity is less than six (6) months, the existing PRH shall first apply for renewal of the registered product.
4) No change(s) can be made to the technical data or approved pharmaceutical/ pharmacological information, including the texts of the product label and leaflet, **except** the name and address of the approved PRH.
5) In the interim, the existing PRH shall still bear the marketing authorization responsibility of the registered product.
6) The transfer shall come into effect on the day the DCA makes a decision on the outcome of the Change of PRH application. Upon the transfer of product registration to the new PRH, the authorization issued to the previous PRH will be cancelled as the product cannot be marketed simultaneously by two different PRHs. The new PRH shall then bear responsibility for the product.

7) However, the existing PRH is still allowed to deplete remaining stocks and will still be held liable for any pharmacovigilance issues or quality defects associated with the product during the interim of the transfer.

8) The existing PRH or newly approved PRH shall submit a written request to deplete the existing stocks after DCA approval has been obtained for the transfer. The PRH that submits the request shall be held responsible for the batches and quantity requested in the event of any pharmacovigilance issues or quality defects associated with those product batches.

9) Application may be rejected if the applicant fails to provide satisfactory required documents within thirty (30) working days starting from the first date of correspondence by the evaluator.

3. SUBMISSION

The existing PRH shall submit the application via the QUEST system and hard copy of original documents to NPRA.

4. PROCESSING FEES

1. NON-REFUNDABLE processing fees:
   - For a Traditional Product : RM 500.00
   - For a Pharmaceutical Product (including Health Supplement) : RM 1,000.00

2. The processing fee shall be paid via the QUEST system immediately after the change of PRH application has been submitted.

5. SUPPORTING DOCUMENTS

5.1 List of required supporting documents:

i) Letter of Authorization (LOA) issued by the Product Owner. **If the Product Owner is an entity registered outside of Malaysia, the LOA must be certified by the Notary Public from the country of origin of said Product Owner. However, if the Product Owner is a Malaysian registered entity, the LOA must be certified by a local Commissioner for Oaths.**

The LOA shall consist of the following information:

a. The registered name and registration number of the product(s) concerned
b. Company name, business registration number and address of the proposed new PRH as registered in QUEST
c. Company name, business registration number and address of the existing PRH as registered in QUEST
d. Effective date of the appointment and termination given by the product owner. If the effective date is not mentioned, the date of the LOA issuance will be considered as the effective date.
e. Signature of the Managing Director/ Director/ President/ Chief Executive Officer/ General Manager who has overall responsibility for the company or organization
f. Full and complete name, address, email address (if available), telephone and fax number (if available) of the Product Owner as registered in QUEST
g. The Product Owner name and address in the LOA must be identical to the information of the Product Owner registered in QUEST for the product(s) concerned.
h. The LOA must be submitted in the Product Owner's official letterhead.

*Note: LOA format example (Please refer to **7.2 Example format for the Letter of Authorization**)

ii) Resolution by the Company Board of Directors of **local Product Owner** verifying that ALL the Board of Directors/ Partners have given their consent to the Change of PRH. This resolution must be signed by ALL the Board of Directors/ Partners. This requirement can be omitted if the Product Owner is not a local entity.

iii) Latest document indicating details of director/s and shareholder/s of **local Product Owner** (e.g. Corporate Information, Summary of Share Capital, Directors/ Officers, Shareholders/ Members from the MyData SSM website). These documents must be certified by the Commissioner for Oaths (i.e. Statutory Declaration). This requirement can be omitted if the Product Owner is not a local entity.

iv) Resolution by the Company Board of Directors of **existing PRH** verifying that ALL the Board of Directors/ Partners have given their consent to the Change of PRH. This resolution must be signed by ALL the Board of Directors/ Partners.

v) Latest document indicating details of director/s and shareholder/s of **existing PRH** (e.g. Corporate Information, Summary of Share Capital, Directors/ Officers, Shareholders/ Members from the MyData SSM website). These documents must be certified by the Commissioner for Oaths (i.e. Statutory Declaration).

vi) The Company/ Business Registration Certificate of the proposed new PRH certified true copy by a MAICSA accredited company secretary or by the Companies Commission of Malaysia (e.g. Form 9 and/ or Form 13).

vii) Statement of Acceptance as Product Registration Holder, *NPRA-430.5(3)* to be filled by the proposed new PRH.

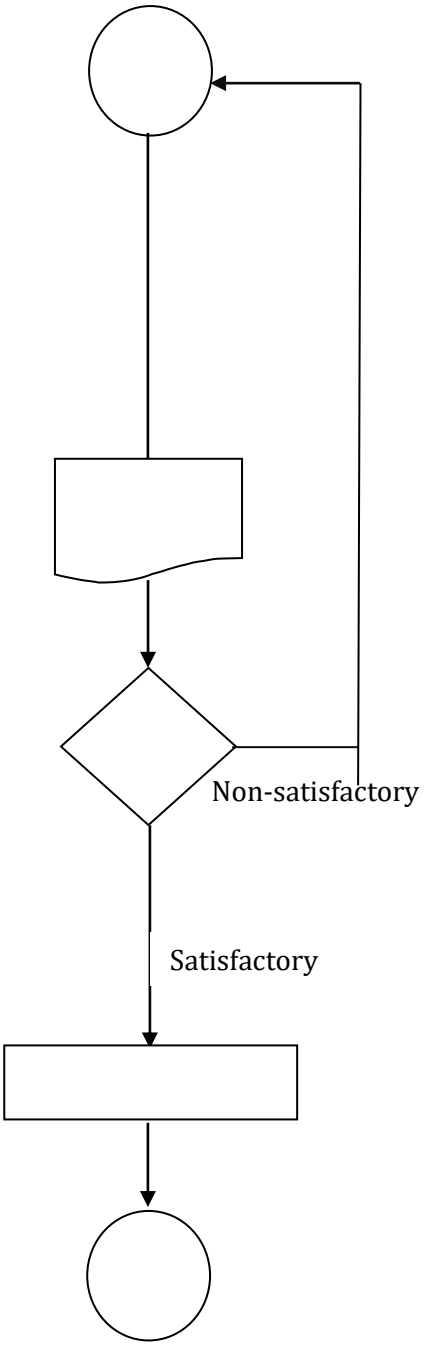
5.2 The ORIGINAL documents listed above shall be submitted to the Centre of Product & Cosmetic Evaluation, NPRA once payment for the application is made. Photocopies of documents will not be accepted.

5.3 Date of the documents including date of stamps/signatures of certifying bodies must be recent, i.e. not exceeding six (6) months from the date of application.

5.4 Each page of attachment (if any), i.e. product list, must be endorsed by the signatory.

5.5 The Secretariat, if necessary, has the right to request further supplementary information or documentation. Failure to provide these additional information or documentation(s) will result in the rejection of the transfer application.

6. CHANGE OF PRODUCT REGISTRATION HOLDER (COH) PROCESS



Company (Existing PRH)

Submit complete application to NPRA;

1. Complete and submit application online via QUEST system
2. Processing Fees (refer to no.4).
3. Submit original supporting documents (refer to no.5) to Centre of Product & Cosmetic Evaluation.

Secretariat

Receive and evaluate application and original documents.

Secretariat

Processing of evaluated application;

1. Satisfactory:
   a) Table to DCA meeting for approval
2. Non-satisfactory:
   b) Table to DCA meeting for rejection (processing fee is NON-REFUNDABLE if application is rejected)

DCA Meeting

Secretariat

Processing of DCA meeting outcome;

1. For approved application: Notification of transfer approval to new proposed PRH and termination notification to existing PRH;
2. For rejected application: Notification of transfer rejection to existing PRH

7. OTHER INFORMATION

7.1 Refer also to Directive No. 4, 2013, *Bil. (3) dlm.BPFK/PPP/07/25*: *Direktif Untuk Meminda Prosedur Permohonan Pertukaran Pemegang Pendaftaran Produk* (3 June 2013)

7.2 Example format for the Letter of Authorization

7.2 Example format for the Letter of Authorization

PRODUCT OWNER Letter Head (full and complete address, email address, telephone and fax number)

(Please state) Date of LOA (the existing PRH shall submit an application within 6 months from this date)

Drug Control Authority,
Lot 36, Jalan Universiti,
46200 Petaling Jaya,
Selangor, Malaysia.

Dear Sir/ Madam,

LETTER OF AUTHORIZATION FOR TRANSFER OF PRODUCT REGISTRATION HOLDER

The above subject matter is referred.

Due to (*please state) reason of the transfer*,

2. We, *Name of registered Product Owner*, the undersigned as the product owner for the said product(s) listed below:

Name of Product(s)	**Registration Number**
(*If number of product > 10, endorsed attachment is allowed.)*	

hereby authorize
Company name with business registration number and full address of the proposed new PRH
to be the Product Registration Holder and to act on our behalf/ responsible for all matters pertaining to the registration of the listed product(s) including obtaining approval for any subsequent product variation and maintenance of the product(s) registration.

3. Therefore, we hereby terminate marketing authorization of the existing Product Registration Holder
Company name with business registration number and full address of the existing PRH
for the listed product(s) effectively on *date of authorization / termination.*

4. We shall confirm that the entire dossier of the listed product(s) includes all the data in support of the original application, together with all correspondence with the Drug Control Authority (DCA)/ National Pharmaceutical Regulatory Division concerning the listed product(s), to be transferred from *Company name of the existing PRH* to *Company name of the proposed new PRH* upon the approval from DCA.

Thank you.

Sincerely,

**Company officer's signature(s)*
**Full name & Title/ Positition*
Company stamp

***Certified by Notary Public/ Commissioner for Oath*

cc: *Company of proposed new PRH*
Company of existing PRH
Product Manufacturer
} *(A copy of LOA shall be sent to these companies by the Product Owner)*

IMPORTANT NOTICE:

1. **LOA shall be signed by Managing Director/ Director/ President/ Chief Executive Officer/ General Manager who has overall responsibility for the company or organization.*
2. ***LOA shall be certified by Notary Public of the country of origin for overseas company or Malaysia Commissioner for Oath for local company.*

APPENDIX 33

EXPLANATORY NOTES FOR REPACKERS

1. INTRODUCTION

This chapter is intended to provide guidance to those engaged in repackaging of finished products with the aim to provide information to any person/ establishments who removes finished products from their original container-closure system and repackages them into a different container-closure system for sale and/ or for distribution.

2. OBJECTIVES

a) To provide uniform guidance and a means of assessing the operations of repackers/ relabelers as they relate to the provisions of the GMP and GDP requirements.
b) To identify the type of repacking activity and whether there is a need to comply with GMP and GDP requirements.

3. DEFINITIONS

Terms	Definitions
Manufacture	Manufacture, in relation to any product includes – a) The making or assembling of the product; b) The enclosing or packing of the product in any container in a form suitable for administration or application, and the labelling of the container and; c) The carrying out of any process in the course of any of the foregoing activities.
Packaging	All operations, including filling & labelling, that a bulk product has to undergo in order to become a finished product. Filling of a sterile product under aseptic conditions or a product intended to be terminally sterilized, would not normally be regarded as part of packaging.

Terms	Definitions
Packaging Material	Any material employed in the packaging of a material or product or cosmetic, including any other packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.
Printed packaging material	Packaging material which is imprinted with text or numbers or a combination of both.
Labelling	The term 'labeling' designates all labels and other written, printed, or graphic matter upon, or in, any package or wrapper in which it is enclosed, except any outer shipping container. A shipping container, unless such container or the outside of the consumer package, is exempted from labelling requirements.
Labeller/ relabeller	A company that affixes the original label to a finished product (i.e labeller) or changes in any way the labelling on a product without affecting the product or its container (i.e. relabeller).
Packaging system	Composed of a container system with its closure. This system may include several layers of protection for the Pharmacopeia preparation along with any sealing devices, delivery devices, labelling and package inserts.
Repacker	A company who removes a finished product from its final packaging and places the finished products into a different container which is labelled or to be labelled before the product is for sale and/or distribution for human use. Repacker may consist of primary and secondary repacker.
Primary repacker	A company who performs repacking activity that places the finished products into a primary/ immediate container which labelled or to be labelled before the product is for sale and/ or distribution for human use.
Secondary repacker	A company who does the repacking activity relating to a) labelling of the product container; and/or b) packing the finished product which is already enclosed in its labelled primary container into a carton which is labelled or to be labelled. before the product is for sale and/ or distribution for human use.

4. EXAMPLES OF TYPES OF REPACKING ACTIVITY

No.	Description of Repacking Activity	Require GMP/GDP Control	Product to be included in Manufacturing License List	Responsibility	Remarks (if any)
1.	Packing/ blistering of imported product (tablet/capsule/liquid/etc.) into a different container	√	√	Primary repacker	
2.	De-blistering of blister strips of tablets/capsules to repack into a new blister pack/container	√	√	Primary repacker	e.g. Blister packs de-blistered and repack into new blister pack due to market purposes, etc.
3.	To form a secondary packaging material (unit box) to pack blister strips, bottles, etc. into this packaging material	√	√	Secondary repacker	e.g. 5 strips in a unit box to be repack to 1 strip in a unit box
4.	To affix an immediate label to a container of product that contains information such as Product Name, Dosage Form, Name of Active Substance(s), Strength of Active Substance(s), Batch Number, Manufacturing Date, Expiry Date, Route of Administration, Storage Condition, etc.	√	√	Primary repacker/ Secondary repacker	Refer to **Appendix 19: General Labelling Requirements** for Immediate Labels
5.	To affix label of outer carton that contains information such as Product Name, Dosage Form, Name of Active Substance(s), Strength of Active Substance(s), Batch Number, Manufacturing Date, Expiry Date, Route of Administration, Storage Condition, etc.	√	√	Secondary repacker	Refer to **Appendix 19: General Labelling Requirements** for Unit Outer Carton

No.	Description of Repacking Activity	Require GMP/GDP Control	Product to be included in Manufacturing License List	Responsibility	Remarks (if any)
6.	To affix country specific label requirements for Malaysia a) Name & content of preservative(s) where present b) The words "Keep medicine out of reach of children" or words bearing similar meaning in both Bahasa Malaysia & English c) The words "Controlled Medicine/ Ubat Terkawal" (For scheduled poisons only) d) Security label (Hologram)	√* √* √* √*	X X X X	Importer/ Primary Repacker/ Secondary Repacker	The importer/ repacker shall maintain the relevant documents (e.g. hologram records, stock card)
7.	To insert new Package Insert/ to change original Package Insert into the inside of the secondary packaging product (unit box)	√	√	Secondary repacker	e.g. Remove Germany package insert from the product and replace with Malaysia specific Package Insert
8.	To attach/ tape Package Insert on the outside of the secondary packaging product (unit box)	√	√	Secondary repacker	
9.	To inkjet the Product Registration Number on the primary/secondary packaging material (unit box)	√	√	Primary/ Secondary repacker	
10.	To inkjet of the Manufacturing Date, Expiry Date and Batch Number on the primary/secondary packaging material (unit box)	√	√	Primary/ Secondary repacker	

No.	Description of Repacking Activity	Require GMP/GDP Control	Product to be included in Manufacturing License List	Responsibility	Remarks (if any)
11.	To affix specific labelling requirement of a product	√	√	Primary/ Secondary repacker	Refer to **Appendix 20: Specific Labelling Requirements**
12.	To inkjet/ affix label 'Sample Not For Sale'/ 'Physician's sample not for sale'/ 'Professional sample not for sale'/ etc. onto the secondary packaging material	√*	X	Secondary repacker/ Importer	
13.	To affix label 'Diimport/diedarkan oleh' onto the primary/ secondary packaging material	√*	X	Primary/ Secondary repacker/ importer	
14.	To affix 'Halal' label onto the primary/ secondary packaging material	√*	X	Primary/ Secondary repacker/ importer	
15.	To shrink wrap several boxes or bottles together	√*	X	Secondary repacker/ Importer	
16.	To repack finished products into tertiary packaging materials without any changes to the product	√*	X	Secondary repacker/ Importer	
17.	To repack several registered finished products as a convenient pack for promotional sale only without changing the product immediate and unit outer carton label	√*	X	Secondary repacker/ Importer	Refer to **20.5 Application for a Convenient Pack**
18.	To affix security seal onto the secondary/ tertiary packaging material	√*	X	Secondary repacker/ Importer	

5. ADDITIONAL NOTES

5.1 √* denotes that the repacking activity has to be done in a Good Distribution Practice (GDP) controlled or licensed facility.

5.2 The repacking activities as listed in Para 4 is non-exhaustive. Product and license holders shall be responsible to ensure that the registered products are repacked in an appropriate manner and all relevant documents is maintained (batch packaging records/logbooks/inventory records/ procedures).

5.3 The conditions of the product must meet the storage requirements as stated in the Good Distribution Practice Guideline by National Pharmaceutical Regulatory Division (NPRA).

5.4 In deciding whether a particular bulk product is suitable for repacking, the repacker should take into consideration any available information from the manufacturer, published literature and any reference pharmacopoeia.

6. REFERENCES

6.1 Good Distribution Practice Guideline
6.2 Control of Cosmetic Products
6.3 USP 31; Volume 1, 2008
6.4 Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics; May 1999
6.5 Irish Medicine Boards Guide to Parallel Imports; AUT-G0006-4.9
6.6 WHO GMP: Main Principles for Pharmaceutical Products.

APPENDIX 34

GUIDELINE ON SAFETY DATA REQUIREMENTS FOR COMPLEMENTARY MEDICINE PRODUCTS

Contents:

1. **Introduction**
2. **Objectives**
3. **Safety Data**
4. **Overview**
5. **Glossary**
6. **References**

1. Introduction

Consumer interest in health and self-care has expanded the market for a wide range of health supplements and traditional products. These categories of products have been used since the earliest history of humanity and have formed one of the foundations for healthcare in cultures throughout the world. With the increased use of such products and the broad spectrum of products classified under this category, it is important to ensure that the products consumed are safe for consumers.

Evaluation of the safety of complementary medicine products (health supplements, herbal products and traditional medicine) must be done in a manner that is cost effective and science-based within the regulatory environment.

Most ingredients might be considered as safe, considering the experience or history of long use. When an ingredient is well known for a specific use, the assessment will be limited to published data (including traditional references). However, under certain conditions, additional data will be required to prove the safety of the product, e.g. for a new active ingredient or a new combination of ingredients. Even if a product has been in use over a long period of time, chronic toxicology risks may have occurred but not recognized.

2. Objectives

This Guideline aims to provide guidance in submitting safety data requirements for assessment to facilitate registration of complementary medicine.

3. Safety Data

Proof that a product is of quality, safe and as efficacious as claimed is a pre-condition for marketing of a complementary medicine product. Safety is dependent upon the overall product formulation, its intended use, dosage, route of administration, duration of use and targeted group where applicable.

Each active ingredient shall make a relevant and reasonable contribution to the overall therapy and the quantity of each active ingredient shall be safe for the recommended use and range of dosage.

3.1 Safety data shall be required to substantiate the safety profile for the following complementary medicine product to be marketed but not limited to:

a. New ingredients
b. Existing active ingredients/products with new combination, new dosage, new delivery system, new methods of manufacturing or for use in a special target population (e.g. pregnant, lactating women, children, etc.).

c. Existing ingredients/products with safety concern. Safety concerns may be newly emerging or established, and in some cases may need additional information to support safe usage in complementary medicine. These safety concerns may be addressed by including additional cautionary statements.

3.2 Safety substantiation might not be required for complementary medicine products that do not fall under items a. - c. as mentioned above. Traditional medicines with documented data; health supplements which have been consumed as food or is a food constituent within the normal usage limit or for those containing ingredients with well documented and established safety profile may also not require further safety substantiation.

Further examples would include:

i) Product containing the same combination (same number of active ingredients) as with another previously registered product with the active ingredients within limits previously registered.

ii) Combination of vitamins and minerals within permissible limits

iii) Formulary products

3.3 Some general principles on assessing product safety shall be as follows:

a) <u>Single ingredient</u>

For well-known ingredients such as vitamins or minerals and herbal ingredients, documented data will be accepted to demonstrate safety of use.

If an ingredient has been used traditionally and documented that it had no safety concerns, the submission of toxicology studies will not be required. However, if history of use is used to support safety, then the details of use must be consistent with its traditional use.

If toxic effects have been reported or there is insufficient documented safety evidence and there are doubts concerning the product/active ingredient, submission of toxicological reports will be required.

In a case when the anticipated intake of this ingredient is significantly higher than the estimated historical intake, or for which the historical intake cannot be assessed, additional safety data/studies will be required.

b) Combination products

There are no special requirements for combinations of well-known ingredients such as vitamins or minerals. Each active ingredient and dosage will be assessed independently and according to documented data.

The intended use/function of each ingredient must support a logical use of the combination in question and if for traditional use must prescribe to the philosophy of that culture. Like acting herbal ingredients are considered to have an additive effect.

Therefore, the dosage of each active substance may be reduced as compared to its single use. The counteracting by one active ingredient to the adverse reaction produced by another must be explained. Illogical combination of herbs or ingredients having widely different therapeutic uses will require justification.

However, for a combination consisting of new active ingredients, toxicological and clinical data for finished product may be requested. This will also apply to new combinations of well-known ingredients. Safety data will have to be on the product with information on individual ingredients as supportive references.

c) Target population

It cannot be assumed that an ingredient is suitable for pregnant or lactating women unless evidence is provided to the contrary. If required, the product should carry the following statement:

"Pregnancy and breastfeeding: Insufficient reliable data"

or

"If you are pregnant /breastfeeding, please consult your doctor/pharmacist before taking this product."

A product will also be generally assumed not safe for children unless proven otherwise. If the product has children dosage instructions, there must be evidence to fully demonstrate safety in children of that age.

4. Overview

Information that will be required to substantiate the safe use of a product may include but is not limited to:

4.1 Literature search

A comprehensive literature search which would include both positive and negative reports must be submitted. The search criteria used should also be mentioned and references cited. Certified translated copies by the recognised bodies must also be provided if the original articles are not in the English or Malay language.

4.2 Extent of use

Information on extent of use in other countries may provide insight into the safety profile. The maximum amount of the ingredient that is recommended or suggested for use as food may be provided as proof of safe use. However, the amount in the product should not exceed the recommended level.

If evidence is to be based on traditional use, it must be clearly stated that the ingredient under review is equivalent to that used traditionally. Knowledge of chemical components of an ingredient will aid in safety evaluation by identifying potentially toxic constituents or constituents known to mimic or modulate endogenous intermediates. Modern extraction methods used may in some instances produce a substance that is compositionally different from those produced using traditional methodology.

The industry should be able to capture the safety data of any abnormalities and or untoward adverse reaction that might be occurred or derived from animal and or human study. Efficacy data will also often include information on adverse events that will be useful in safety evaluation.

Evidence of the regulatory status of the product in other countries may also be provided as supportive evidence to justify safe use of the product.

4.3 Pharmacological properties

This would include pharmacodynamic and pharmacokinetic studies for medicinal use except for traditional products which will be based on the philosophy of its traditional use.

4.4 Toxicology data

The intended use and the duration of use whether it is for short or long term use will also determine the type of toxicity data needed, e.g acute and/or chronic toxicity. Other toxicity data which should be identified would include teratogenicity, carcinogenicity and mutagenicity data, where necessary. All evidence, both favorable and unfavorable should be included.

Toxicity data could be derived from sources such as authoritative reference test or from animal and/or human study. The Organisation for Economic Co-operation and Development (OECD) Guidelines shall be used as a guide to conduct toxicity study on animals.

4.5 Human data

Safety profile of an ingredient may be obtained from sufficiently powered prospective observational studies, clinical trials, dose-escalation studies, systematic reviews, retrospective meta-analysis studies or even observation of adverse events under controlled studies.

4.6 Post marketing surveillance

Premarket safety studies are sometimes limited by the number of study subjects. When products are in wide use, detection of adverse events provides a strong surrogate for safety monitoring in the general population and in consumers who have chronic conditions. Post marketing surveillance also provides valuable information about a product's safety profile in vulnerable populations e.g. in pregnancy, lactation, the elderly etc.

Interaction with other medications/ supplementation or even food has significant safety implications because of their effects on bioavailability or induction/inhibition of metabolizing enzymes. Such interaction may lead to synergism or antagonism of intended effects.

Safety concerns from existing products may come from the reporting of the adverse reaction monitoring mechanism in the market or through post market control.

The industry and regulator may collect those data from post-market reporting and should assess the causality between the emerging safety concern and the product.

5. Glossary

5.1 New ingredient

New ingredient refers to complementary medicine active ingredient/excipient that has never been listed in the QUEST database.

5.2 New delivery system

New delivery system involves a change in the method of administration and/or the physical dosage form of a complementary medicine product.

5.3 New combination

A combination product, even if it consists of only existing ingredients, is regarded as a *New Combination*, when no product of the same composition (in terms of the constituent ingredients and their relative quantities if higher than documented limits) had been approved for marketing in Malaysia before.

5.4 New dosage

New dosage refers to the quantity of ingredients/ substances to be used in a daily dose as well as single dose basis, if higher than documented limits.

5.5 Recognised bodies (with reference to translation of documents)

Certified translators, embassies, Malaysia Pharmaceutical Society (MPS), Malaysian Organisation of Pharmaceutical Industries (MOPI), Pharmaceutical Association of Malaysia (PhAMA), Malaysian Dietary Supplement Association (MADSA), Federation of Chinese Physicians & Medicine-Dealers Association of Malaysia (FCPMDAM), Federation of Chinese Physicians & Acupuncturists Association of Malaysia (FCPAAM), Malaysian Chinese Medical Association (MCMA), Direct Selling Association of Malaysia (DSAM), Malaysian Direct Distribution Association (MDDA), Persatuan Pengeluar Ubat Tradisional Malaysia (PURBATAMA), Gabungan Pertubuhan Pengamal Perubatan Tradisional Melayu Malaysia (GAPERA), Malaysian Homeopathic Medical Council (MPHM), Malaysian Association of Traditional Indian Medicine (PEPTIM), and related industry associations of the country of origin recognized by the local authority.

6. References

1. World Health Organization. General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine, 2000.
2. World Health Organization. Guidelines for the regulation of herbal medicines in the South-East Asia Region, 2003.
3. WHO Research Guideline for The Evaluation of Safety and Efficacy of Herbal Medicine 1993.
4. Organization for Economic Cooperation and Development (OECD) Guideline for toxicity studies in animals. Webpage: *www.oecd.org*
5. Therapeutic Goods Administration, Australia; Webpage: *www.tga.gov.au*
6. Health Canada; Webpage: *www.hc-sc.gc.ca/index-eng.php*
7. European Medicines Agency; Webpage: *www.emea.eu*
8. Medicines and Healthcare Products Regulatory Agency (MHRA); Webpage: *www.mhra.gov.uk*
9. ASEAN Traditional medicine and Health supplement Product Working Group (TMHS PWG) Meeting minutes