APPENDIX 2: REQUIREMENTS FOR PRODUCT REGISTRATION

IMPORTANT NOTES:

1. This appendix is for reference purpose only, where applicable, and it may not follow the sequence as 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, whichever it may deems fit.

This appendix comprises of two (2) parts which are:

2.1 General requirements for:

2.1.1 Full Evaluation;
(In accordance to ASEAN ACTD/ ACTR or ICH guidelines)

- 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)

2.1.2 Abridged Evaluation.

2.1.3 Additional Information on Requirement of:

- Bioavailability (BA) Study
- Bioequivalent (BE) Study

2.2 Product Specific Requirements

2.1 GENERAL REQUIREMENTS

Data to be submitted as general requirement to support an application for product registration is based on the product category as shown below:

(A) FULL EVALUATION (based on ACTD/ ACTR)					
No.	**Product Category**	**Part I**	**Part II**	**Part III**	**Part IV**
1.	New Drug Products	√	√	√	√
2.	Biologics	√	√	√	√
3.	Generics (Scheduled Poison)	√	√	Not Applicable	Not Applicable
4.	Generics (Non-Scheduled Poison)	√	√	Not Applicable	Not Applicable
5.	Health Supplements: Disease Risk Reduction Claims (High)	√	√	√	√

(B) 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) which are evaluated under abridged evaluation include, but 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.

2.1.1 GENERAL REQUIREMENTS FOR FULL EVALUATION

No.	Step I: Product Validation
1.	Is your product has a brand name? (Yes/ No) (If yes, please provide brand name and 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)
6.	Manufacturer (Name and Address)
7.	Is the selected manufacturer a contract manufacturer? (Yes/ No)
8.	Is the product from second source? (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 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)

No.	Step I: Product Validation
10.	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
11.	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
12.	Is this an imported product? (Yes/ No)

Step II:	
Part I: Administrative Data And Product Information	
No.	**Section A: Product Particulars**
1.	Product Name
2.	Name & Strength of Active Substance and 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.	Storage Condition
17.	Shelf Life

Step II:	
18.	Therapeutic Code/ ATC Code
No.	**Section B: Product Formula**
1.	Batch Manufacturing Formula
2.	Attachment of Batch Manufacturing Formula Documentation
No.	**Section C: Particulars of Packing** - Please refer Appendix 10: Guide for Implementation of Patient Dispensing Pack for Pharmaceutical Products in Malaysia
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)
No.	**Section D: Label (Mock-up) For Immediate Container, Outer Carton, Proposed Package Insert** - Please refer Appendix 9: Labelling Requirements
1.	Proposed Label Mock-up for Immediate Container
2.	Proposed Label Mock-up for Outer Carton
3.	Proposed Package Insert
No.	**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)
5.	Is the active ingredient(s) patented in Malaysia? (Yes/ No) (If yes, please attach the related document)
6.	Certificate of Pharmaceutical Product (CPP)

Step II:	
7.	CPP Issuing Body
8.	Is this product licensed to be placed on the market for use in the exporting country? (Yes/ No) (If no, please state the reason)
9.	Is the product on the market in the exporting country? (Yes/ No) (If no, please state the reason)
10.	Date of Issue of CPP
11.	Date of Expiry of CPP
12.	Certificate of Free Sale (CFS)
13.	CFS Issuing Body
14.	Date of Issue of CFS
15.	Date of Expiry of CFS
16.	Certificate of Good Manufacturing Practice (GMP)
17.	Certificate of GMP Issuing Body
18.	Date of Issue of Certificate of GMP
19.	Date of Expiry of Certificate of GMP
20.	Summary of Product Characteristics (Product Data Sheet)
21.	Consumer Medication Information Leaflet (RiMUP) [Previuosly known as Patient Information Leaflet (PIL)]
22.	***Attachment of Protocol Analysis**
23.	***Attachment of Analytical Validation**
24.	***Certificate of Analysis (CoA)**
25.	Other Supporting Document (if any)
26.	Manufacturer (Name and address)
27.	Importer (if any)
28.	Other manufacturer(s) involved, e.g. repacker (if any) (Please attach Certificate of GMP, if yes)
29.	Store Address
PART II: QUALITY OF PRODUCT	
No.	**Section P: Drug Product (Finished Product)**
1.	Description and Composition

Step II:	
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 Manufacturing Formula
	b) Manufacturing Process and Process Controls
	c) Manufacturing Process Flowchart
	d) Control of Critical Steps & Intermediates
	e) Process Validation and/or Evaluation
4.	Control of Excipients
	a) Specifications
	b) Analytical Procedures
	c) Validation of Analytical Procedures
	d) Justification of Specifications
	e) Excipient of Human or Animal Origin
	f) Novel Excipients
5.	Control of Finished Products
	a) Specifications
	b) Analytical Procedures
	c) Validation of Analytical Procedures
	d) Batch Analyses
	e) Characterization of impurities
	f) Justification of Specifications
6.	Reference Standards or Materials

Step II:	
7.	Container Closure System
8.	Stability
9.	Product Interchangeability/ Equivalent Evidence (Bioavailability/ Bioequivalence, BA/BE) - *Please refer 2.1.3 Additional information on requirements of BA and BE.*
No.	**Section S: Drug Substance**
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
6.	Container Closure System

Step II:	
7.	Stability
PART III: NONCLINICAL DOCUMENT	
	Section A: Table of Contents
No.	**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
No.	**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
No.	**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 and Latest Periodic Safety Update Report (PSUR)

Notes:

* Evaluated by Centre for Quality Control. For details, please refer to Section C: Quality Control in the main DRGD.

2.1.2 GENERAL REQUIREMENTS FOR ABRIDGED EVALUATION

No.	Step I: Product Validation
1.	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)
6.	Manufacturer (Name and Address)
7.	Is the selected manufacturer a contract manufacturer? (Yes/ No)
8.	Is the product from second source? (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 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)

No.	Step I: Product Validation
10.	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
11.	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
12.	Is this an imported product? (Yes/ No)

Step II:	
No.	**Section A: Product Particulars**
1.	Product Name
2.	Product Description
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 Indication/ Usage
5.	Dose/ Use Instruction
6.	Contraindication
7.	Warning and Precautions
8.	Drug Interaction
9.	Side Effects/ Adverse reaction
10.	Signs and Symptoms of Overdose and Treatment
11.	Storage Condition
12.	Shelf Life
13.	Therapeutic Code/ ATC Code
No.	**Section B: Product Formula**

Step II:	
1.	Batch Manufacturing Formula a) Batch Size b) Unit
2.	Active Ingredients a) Active Ingredients Name b) Quantity c) Source d) Form of Substance e) Overage (%) f) Remarks
3.	Excipients a) Active Ingredients Name b) Quantity c) Function d) Source e) Overage (%) f) Remarks
4.	Attachment of Batch Manufacturing Formula Documentation
5.	Manufacturing Process
6.	Attachment of Manufacturing Process Documentation
7.	In-Process Quality Control
8.	Attachment of Finished Product Specification Documentation
9.	Attachment of Stability Data Documentation *(For two batches) - Compulsory for imported product*
No.	**Section C: Particulars of Packing** - Please refer Appendix 10**:** Guide for Implementation of Patient Dispensing Pack for Pharmaceutical Products in Malaysia
1.	Pack Size (Fill details by weight/ volume/ quantity) Measurement Type
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)

Step II:	
6.	Other Related Attachment (if any)
No.	**Section D: Label (Mock-up) For Immediate Container, Outer Carton, Proposed Package Insert** - Please refer Appendix 9: Labelling Requirements
1.	Proposed Label Mock-up for Immediate Container
2.	Proposed Label Mock-up for Outer Carton
3.	Proposed Package Insert
No.	**Section E: Particulars of Product Owner, Manufacturer, Importer and Other Manufacturer(s) Involved and Store address**
1.	Product Owner
2.	Manufacturer
3.	Other Manufacturer(s) involved (if any) a) Manufacturer Name and Address b) Processing Steps Involved c) Certificate of Good Manufacturing Practice (GMP)
4.	Store Name and Address
5.	Importer
No.	**Section F: Supplementary Documentation**
1.	Letter of Authorization from Product Owner
2.	Letter of Appointment of Contract Manufacturer from Product Owner (if applicable)
3.	Letter of Acceptance from Contract Manufacturer (if applicable)
4.	Is the active ingredient(s) patented in Malaysia? (If yes, please attach the related document)
5.	Certificate of Pharmaceutical Product (CPP)
6.	CPP Issuing Body
7.	Is this product licensed to be placed on the market for use in the exporting country? (If no, please state the reason)
8.	Is the product on the market in the exporting country? (If no, please state the reason)
9.	Date of Issue of CPP

Step II:	
10.	Date of Expiry of CPP
11.	Certificate of Free Sale (CFS) (if any)
12.	CFS Issuing Body
13.	Date of issue of CFS
14.	Date of expiry of CFS
15.	Certificate of Good Manufacturing Practice (GMP)
16.	Certificate of GMP Issuing Body
17.	Date of issue of Certificate of GMP
18.	Date of expiry of Certificate of GMP
19.	Summary of Product Characteristics (Product Data Sheet)
20.	Consumer Medication Information Leaflet (RiMUP) [Previously known as Patient Information Leaflet (PIL)]
21.	Attachment of Protocol Analysis
22.	Attachment of Certificate of Analysis (CoA) *(For two batches)* ** Compulsory for imported products*
23.	Attachment of Specifications and Certificate of Analysis of Active Ingredient
24.	Other Supporting Documents (if any)

2.1.3 ADDITIONAL INFORMATION ON:

A) BIOAVAILABILITY (BA) STUDY

For modified-release products, dosage recommendations and regime must be supported by bioavailability studies.

Studies comparing availability or establishing equivalence of similar products would be useful.

B) BIOEQUIVALENCE (BE) STUDY

Note: *This requirement is applicable to generics (scheduled poison) only.*

With the increasing availability of generic products, a mechanism is required to ensure that such products are therapeutically equivalent to the innovators' products and are clinically interchangeable.

In practice, demonstration of bioequivalence (BE) is generally the most appropriate method of substantiating therapeutic equivalence between medicinal products. A list of drug substances, which, when formulated in oral solid dosage forms, require BE data as a prerequisite for registration, has been established by the authority (please refer to NPRA website at http://npra.moh.gov.my/). This list is updated based on the requirements.

Bioequivalence (BE) Study Requirements for Generic Product in Immediate Release, Oral Solid Dosage Form Submitted as a Second Source Application

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 can be considered, provided that Comparative Dissolution Profile (CPD) report against the registered first source product is submitted as a surrogate to bioequivalence study conducted for the second source product and all the following conditions shall be fulfilled:

a) Bioequivalence study conducted using the registered first source product has been evaluated by the NPRA and found satisfactory.

b) The second source product is the same as registered first source product used in the bioequivalence study in terms of:

   i) Product formulation;
   ii) Equipment used in the manufacturing process;
   iii) Source and supplier of raw material;
   iv) Quality control and specifications of raw material;
   v) Manufacturing process of product and standard operating procedures;
   vi) Environmental conditions during the manufacturing process of product;
   vii) Quality control and specifications of finished product.

c) Comparative Dissolution Profile must be conducted in accordance to ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies including the calculation of similarity factor (f2) to prove the similarity of these two products.

d) Process validation has been conducted on 3 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.
(Reference: Circular Bil.(10)dlm.BPFK/PPP/07/18Jld.1 *, 2 Jun 2011)*

Starting on 1st of January 2012, bioequivalence (BE) study is required for all application of registrations for generic products containing scheduled poison in the form of immediate release, oral, solid dosage form whereas renewal of registered products, the effective date is on 1st January 2013.
(Directive *Arahan di Bawah Peraturan 29, Peraturan-peraturan Kawalan Dadah dan Kosmetik 1984 Bil. 1 Year 2011*, 2 March 2011 Bil (10) dlm BPFK/PPP/01/03 Jld 1)

Sponsors or BE study centers are compulsory to notify the Authority pertaining to all BE studies which do not require Clinical Trial Import Licence (CTIL) or Clinical Trial Exemptions (CTX) and are going to be done at either local or overseas BE study centers for registered products or products to be registered in Malaysia (Directive *Arahan di Bawah Peraturan 29, Peraturan-peraturan Kawalan Dadah dan Kosmetik 1984 Bil. 13 Year 2011*, 14 October 2011, Bil (23) dlm BPFK/PPP/01/03 Jld 1).

Note: The two above directives shall be read in conjunction with the supplementary circular that further explains the procedure for evaluation of BE centre inspection

reports in line with the requirement of accreditation of BE Centres. (Reference: Circular dated 12 September 2013; Bil(6)dlm.BPFK/PPP/01/03 Jld 3.)

Effective 1st March 2013, biowaiver may be granted to generic immediate release oral solid dosage form products containing BCS Class I active ingredients listed in the Guidance On Biopharmaceuticals Classification System (BCS) – Based Biowaiver document. BCS Based biowaivers takes the three major factors that govern the rate and extent of drug absorption from immediate-release solid dosage forms into accounts i.e. solubility and permeability of the drug substance/ API, and dissolution characteristics of the dosage form. This BCS approach provides an opportunity to waive *in vivo* pharmacokinetic bioequivalence testing for certain categories of immediate-release drug products.
(Directive *Arahan di Bawah Peraturan 29, Peraturan-peraturan Kawalan Dadah dan Kosmetik 1984 Bil. 1 Year 2013*, 14 October 2011, 28 February 2013, Bil (101)dlm.BPFK/PPP/01/03 Jld 2).

For more information on BE, please refer Bioequivalence (BE).

2.2 SPECIFIC REQUIREMENTS

For biologics, health supplements and natural products, please refer guidelines for the respective product category at:

a) Appendix 3: Guidelines on Registration of Biologics
b) Appendix 4: Guideline on Registration of Health Supplements
c) Appendix 5: Guideline on Registration of Natural Products

Please refer as well on **Appendix 11**: Guideline on Filling the Online Application Form for Product Registration via Quest System before submission of an application for product registration.