Malaysian Guideline *for* Application of Clinical Trial Import Licence and Clinical Trial Exemption

National Pharmaceutical Regulatory Agency (NPRA)
Ministry of Health Malaysia

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MALAYSIAN GUIDELINE FOR APPLICATION OF CLINICAL TRIAL IMPORT LICENCE AND CLINICAL TRIAL EXEMPTION

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ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
ARC	Annual Retention Certificate
ASEAN	Association of Southeast Asian Nations
BE	Bioequivalence
CDCR	Control of Drugs and Cosmetics Regulations
CIOMS	The Council of International Organisation for Medical Science
CoA	Certificate of Analysis
CGTP	Cell and Gene Therapy Product
CRO	Contract Research Organisation
CSR	Clinical Study Report
CTIL	Clinical Trial Import Licence
CTX	Clinical Trial Exemption
CV	Curriculum Vitae
DCA	Drug Control Authority
DCT	Decentralised Clinical Trial
DHT	Digital Health Technology
DPS	Director of Pharmaceutical Services
EC	Independent Ethics Committee/ Institutional Review Board
EMA	European Medicines Agency
FIH	First-in-Human
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IP	Investigational Product
IPESS	Investigational Product Evaluation and Safety Section
NCCR	National Committee for Clinical Research
NDRA	National Drug Regulatory Authority
NHRVR	National Healthy Research Volunteer Register
NMRR	National Medical Research Register
NPRA	National Pharmaceutical Regulatory Agency
NRIC	National Registration Identity Card
PD	Pharmacodynamics
PI	Principal Investigator

PIC/S	Pharmaceutical Inspection Co-operation Scheme
PK	Pharmacokinetic
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Drug Reaction
TGA	Therapeutic Goods Administration
US FDA	United States Food and Drug Administration
WHO	World Health Organization
WMA	World Medical Association

GLOSSARY

Accuracy
The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found. This is sometimes termed trueness.

Active Substance
Any substance or mixture of substances intended to be used in the manufacture of an investigational product and that, when used in its production, becomes an active ingredient of that product which is intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions, or to make a medical diagnosis.

Adverse Drug Reaction
In the pre-approval clinical experience with an investigational product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to an investigational product related to any dose should be considered adverse drug reactions (ADR). The phrase "responses to an investigational product" means that a causal relationship between an investigational product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Regarding a marketed product, an adverse drug reaction is a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.

Adverse Event
Any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

Analytical Procedure
The analytical procedure refers to the way of performing the analysis. It should describe in detail the steps necessary to perform each analytical test. This may include, but is not limited to: the sample, the reference standard and the reagents preparations, use of the apparatus, generation of the calibration curve, use of the formulae for the calculation, etc.

Approved Training in Good Clinical Practice
Training which is approved by the National Committee for Clinical Research. The content of the training must incorporate the curriculum as stipulated by the committee.

Auxiliary Product
A medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational products being tested/ comparator. For example, standard of care, rescue medication, pre-medication and concomitant drug.

CIOMS Form
A form for reporting ADR according to The Council of International Organisation for Medical Science.

Clinical Trial Exemption
An exemption issued under regulation 15 (5), Control of Drugs and Cosmetics Regulations 1984 by the Director of Pharmaceutical Services, which exempts a person who wishes to manufacture product(s) solely for the purpose of producing samples for clinical trials from the provisions of regulation 7 (1) or regulation 18A of Control of Drugs and Cosmetics Regulations 1984.

Clinical Trial Import Licence
A licence in Form 4 in the Schedule of the Control of Drugs and Cosmetics Regulations 1984, issued by the Director of Pharmaceutical Services under regulation 12(1)(*c*) of the same Regulations which authorises the licensee to import any product for the purposes of clinical trials, notwithstanding that the product is not a registered product.

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 objective of ascertaining its safety and/or efficacy. The terms 'clinical trial' and 'clinical study' are synonymous.

Generally, clinical trials can be categorised in 4 phases.

- For phase 1 trials, the aim is to determine the safety and tolerance of the investigational product. Examples of Phase 1 trials include first-in-human (FIH) studies, pharmacokinetics and pharmacodynamics studies, and drug-drug interaction studies. The number of subjects involved are usually small numbers of healthy volunteers or patients (10-100 subjects).
- For phase 2 trials, the aim is to determine the efficacy and safety of the investigational product. Phase 2 trials explore the therapeutic dose range of the investigational product to treat a disease or condition and gathering more information on the investigational products' safety in a larger group of patients (100-300 subjects).
- For phase 3 trials, the aim is to determine the safety, efficacy or effectiveness of the investigational product. Phase 3 trials are confirmatory trials conducted to determine the therapeutic effect in patient populations for which the investigational product is intended. They also provide a definitive assessment of risk-benefit balance (to support drug registration or change in clinical practice). The number of subjects involved usually includes a large group of patients, ranging from several hundred to several thousand (300-3000 subjects).
- For phase 4 trials, the aim is to conduct a post-marketing surveillance to monitor safety in real-world populations, including the long-term benefits and risks of the product. These trials take place after the product is approved and is on the market, and usually involve a large group of patients (1000 subjects).

Clinical Trial/Study Report
A written description of a trial/study of any therapeutic, prophylactic, diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the ICH Guideline for Structure and Content of Clinical Study Reports).

Comparator (Product)
An investigational or marketed product (i.e. active control), or placebo, used as a reference in a clinical trial.

Confidentiality
Prevention of disclosure to other than authorised individuals of a sponsor's proprietary information or of a subject's identity.

Contract
A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

Contract Research Organisation
A person or an organisation (commercial, academic, or other) contracted by a sponsor to perform one or more of the sponsor's trial-related duties and functions.

Decentralised Clinical Trial
A clinical trial where some or all of the trial-related activities occur at locations other than traditional clinical trial sites.

Detection Limit
The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value.

Digital Signature
A transformation of a message using an asymmetric cryptosystem such that a person having the initial message and the signer's public key can accurately determine
(a) whether the transformation was created using the private key that corresponds to the signer's public key; and
(b) whether the message has been altered since the transformation was made.

Drug Control Authority
An authority set up under the Control of Drugs and Cosmetics Regulations 1984 and as such its responsibility, role, and mandate are defined by law.

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 medicinal purposes.

First-in-Human
First-in-human (FIH) studies start with the initial administration of a novel active ingredient into humans. Traditionally, FIH studies were most associated with a single ascending dose (SAD) design, which was subsequently followed by a multiple ascending dose (MAD) design. FIH studies include clinical trials with a higher dose that has yet to be tested in humans.

Good Clinical Practice
A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

Herbal Medicinal Products
Herbal medicinal 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 substances have been added, including synthetic compounds and/or isolated

constituents from herbal materials, are not considered to be herbal.

Independent Ethics Committee
An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical/scientific professionals and non-medical/non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favourable opinion on the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects. The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ between countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in Malaysian Guideline for GCP.

Informed Consent
A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

Inspection
The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial that may be located at the site of the trial, at the sponsor's and/or contract research organisation's facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

Institution (medical)
Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

Institutional Review Board
An independent body constituted of medical, scientific, and non-scientific members whose responsibility is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing a continuing review of the trial protocol and amendments, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

Interim Clinical Trial/Study Report
A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

Investigational Product
A pharmaceutical form of an active ingredient or placebo, being tested or used as a reference in a clinical trial, including a product with a marketing authorisation, when used or assembled (formulated or packaged) in a way different from the approved form.

Investigator
A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

Investigator's Brochure
A compilation of the clinical and non-clinical data on the investigational product(s) which is

relevant to the study of the investigational product(s) in human subjects.

Linearity
The linearity of an analytical procedure is its ability (within a given range) to obtain test results which are directly proportional to the concentration (amount) of analyte in the sample.

Manufacture
All operations of purchase of materials and products, production, quality control, release, storage, shipment (from storage related to manufacturing site) of finished products, and related controls.

Manufacturer
A company that carries out at least one step of production as well as the final release of the finished product.

Medicinal Purpose
Any of the following purposes are deemed medicinal purpose:
a. Alleviating, treating, curing, or preventing a disease, 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 well-being.

Multicentre Trial
A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

National Committee for Clinical Research
A committee established to coordinate and promote clinical research in Malaysia, chaired by the Director General of Health, Ministry of Health.

Opinion (in relation to Independent Ethics Committee)
The judgement and/or the advice provided by an ethics committee.

Placebo
A control substance (a dummy treatment) that is given to people taking part in a clinical trial. It allows researchers to test for the 'placebo effect'. This is a psychological response where people feel better even though the substance they are taking has no effect. By comparing people's responses to the placebo and the drug being tested, researchers can tell whether the drug is having any real benefit.

Poison
Any substance specified by name in the first schedule of the Poisons List and includes any preparation, solution, compound, mixture, or natural substance containing such substance, other than an exempted preparation or an article or preparation included for the time being in the Second Schedule.

Product
a. 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;

b. A drug to be used as an ingredient for preparation of a medicinal purpose.

Protocol
A document that describes the objective(s), design, methodology, statistical considerations, and organisation of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol-referenced documents. Throughout the Malaysian Guideline for Good Clinical Practice, the term protocol refers to protocol and protocol amendments.

Protocol Amendment
A written description of a change(s) to or formal clarification of a protocol.

Quality Assurance
All those planned and systematic actions that are established to ensure that the trial is performed, and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice and the applicable regulatory requirement(s).

Registered/Approved Product
Any product which is registered with the Drug Control Authority.

Regulatory Authority
Bodies having the power to regulate. In the Malaysian Guidelines for Good Clinical Practice the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections. These bodies are sometimes referred to as competent authorities.

Repeatability
Repeatability expresses the precision under the same operating conditions over a short interval of time. Repeatability is also termed intra-assay precision.

Serious Adverse Event or Serious Adverse Drug Reaction
Any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

Specificity
The ability to assess unequivocally the analyte in the presence of components which may be expected to be present. Typically, these might include impurities, degradants, matrix, etc.

Lack of specificity of an individual analytical procedure may be compensated by other supporting analytical procedure(s).

This definition has the following implications:

Identification:	To ensure the identity of an analyte.
Purity Tests:	To ensure that all the analytical procedures performed allow an accurate statement of the content of impurities of an analyte, i.e. related substances test, heavy metals, residual solvents content, etc.
Assay (content or potency):	To provide an exact result which allows an accurate statement on the content or potency of the analyte in a sample.

Sponsor
An individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial.

Trial Site
The location(s) where trial-related activities are actually conducted.

Unexpected Adverse Drug Reaction
An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., investigator's brochure for an unapproved investigational product or package insert/summary of product characteristics for an authorised product).

Unregistered Product
Any product which is not registered with the Drug Control Authority.

Vaccine
Medicinal products intended for prevention, post-exposure prophylaxis and/or treatment of disease caused by an infectious agent and which contain antigen(s) or genetic information for an antigen(s), either of biological or synthetic nature, that induce a specific immune response against the causative infectious agent(s) or its toxins.

Vaccines for human use include one or more of the following:
- Organisms that have been inactivated by chemical or physical means;
- Live organisms that are naturally non-virulent in humans or that have been treated or genetically modified to attenuate their virulence;
- Antigens extracted from pathogens or secreted by them, which may be used in their native state, detoxified by chemical or physical treatments or aggregated, polymerised or conjugated to a carrier to increase their immunogenicity;
- Antigens produced by genetic engineering or chemical synthesis;
- Live bacterial or viral vector vaccines expressing foreign antigens;
- Nucleic acid, including plasmids engineered to express specific antigens

SECTION I

1. Introduction

This guideline is intended to assist the applicant in making a CTIL/CTX application to the NPRA and reporting to the NPRA during and at the end of a clinical trial.

This guideline is issued by the Director of Pharmaceutical Services (DPS) under regulation 29, Control of Drugs and Cosmetics Regulations (CDCR) 1984. This guideline is to be read in connection with the legal requirements of the CDCR 1984, Sale of Drugs Act 1952 and Poisons (Psychotropic Substances) Regulations 1989.

Under Regulation 7(1), CDCR 1984, except as otherwise provided in these Regulations, no person shall manufacture, sell, supply, import, possess, or administer any product unless the product is a registered product and the person holds the appropriate licence required and issued under these Regulations. The regulations below provide the mechanisms that allow individuals to gain limited access to unregistered products for clinical trials:

Regulation 12(1)(c): Clinical Trial Import Licence (CTIL)

A Clinical Trial Import Licence in Form 4 in the Schedule, authorising the licensee to import any product for purposes of clinical trials, notwithstanding that the product is not a registered product.

Regulation 15(5): Clinical Trial Exemption (CTX)

Any person who wishes to manufacture any products solely for the purpose of producing samples for clinical trials, for registration or issuance of notification note under these Regulations may on application be exempted by the DPS from the provisions of regulation 7(1) or regulation 18A.

For a clinical trial involving products that require CTIL/CTX, the trial cannot commence until the ethics committee (EC) issues a favourable opinion and the CTIL/CTX application is approved by the NPRA.

Following the WHO Regulatory System Assessment in November 2023, the practice of sharing CTIL/CTX between clinical trials will be discontinued. Therefore, CTIL/CTX will now be issued specifically for each product for the respective study protocols and cannot be shared. This requirement is applicable for new CTIL/CTX applications.

All clinical trials conducted in Malaysia shall comply with the Malaysian Guideline for Good Clinical Practice as well as the legal, ethical, and regulatory requirements of Malaysia.

2. Registration of Clinical Trial with National Registers

2.1 National Medical Research Register (NMRR)

All clinical trials requiring CTIL/CTX must be registered with the National Medical Research Register (NMRR). Reference is made to the Directive of KKM-5512011005101 (11). The CTIL/CTX application may be submitted concurrently with NMRR registration. However, the applicant must provide the NMRR ID for the approval of the CTIL/CTX evaluation.

2.2 National Healthy Research Volunteer Register (NHRVR)

For clinical trials that involve healthy volunteers, it is the responsibility of the sponsor or applicant to register the healthy volunteers in the NHRVR database as per the directive of DPS CTI-2021. Reference is made to the Directive NPRA.600-1/9/13 (27).

3. Products that Require CTIL/CTX

Before commencing any clinical trial involving unregistered product(s) that require CTIL/CTX, and prior to importing or manufacturing the product locally for the trial, the CTIL/CTX must first be obtained.

The following products require a CTIL/CTX:

3.1 An unregistered product, including a placebo, imported/manufactured locally for the clinical trial.

3.2 A product with a marketing authorisation when assembled (formulated or packaged) in a way different from the approved form; AND when used for unapproved indication or when used to gain further information about an approved use, for clinical trial purposes.

3.3 A traditional product with a marketing authorisation with an indication for "traditionally used", when used for an unapproved therapeutic claim in a clinical trial.

The category of product(s) applicable for CTIL/CTX application includes new chemical entities, biologics (including vaccines and Cell and Gene Therapy Products), generics, health supplements, and herbal products. If uncertainty arises regarding the product category, the applicant may apply for classification of product with the Product and Cosmetic Regulatory Coordination Section at the Centre of Regulatory Coordination and Strategic Planning, NPRA.

4. Application Formalities for CTIL/CTX

4.1 Who can apply

4.1.1 An investigator

4.1.2 An authorised person from a locally registered pharmaceutical company, sponsor, or contract research organisation (CRO) with a permanent address in Malaysia.

Note:

- Applications for CTIL/CTX containing poison must be made by a Poison Licence Type A holder for pharmacists in a private sector, or Annual Retention Certificate (ARC) holder for public pharmacists.

- The holder of CTIL/CTX need not necessarily conduct the clinical trial himself or herself.

4.2 Responsibilities of the applicant

4.2.1 The applicant is responsible for the product and all information provided in support of the CTIL/CTX application. The applicant is responsible for updating any information relevant to the product or the application.

4.2.2 In cases where the applicant is not the manufacturer and confidentiality prevents the

disclosure of specific information to the applicant, said information may be submitted directly to NPRA through the applicant in a sealed envelope and appropriately marked as 'CONFIDENTIAL'.

4.2.3 Any individual knowingly supplying false or misleading information in connection with their application for CTIL/CTX commits an offence under Regulation 13(4), CDCR 1984.

4.3 Submission and screening

The applicant must request for online screening from the Head of Investigational Product Evaluation and Safety Section, Centre of Product and Cosmetic Evaluation. The screening officer will inform the applicant of the date of the document received by email. The applicant will be informed of the results within 7 working days.

Upon successful online screening, the applicant is required to proceed to the Finance, Accounts & Revenue Section to complete the payment for CTIL application. The applicant is then required to provide a hardcopy dossier and the official receipt (CTIL application) to screening officer for verification in order for the application to be accepted for evaluation.

Please refer to the flowchart in Section 5.1 Flow chart for the CTIL/CTX application.

4.4 Documents to be submitted

4.4.1	**Table of contents** A contents page must be included in each CTIL/CTX application dossier. A template table of contents can be found in Appendix A.
4.4.2	**Cover letter** A signed cover letter must be submitted with the application. Its subject line should contain the full NMRR Registration Number (if available) and the protocol number, along with the title of the trial. In the cover letter, the applicant should draw attention to peculiarities of the trial, if any.
4.4.3	**CTIL/CTX application form** A complete application form must be submitted. The application form must be signed and dated by the applicant and stamped with the company's stamp. Digital signature according to the Digital Signature Act 1997 is acceptable. Application forms for CTIL (Form No. NPRA/427/01) and CTX (Form No. NPRA/427/02) can be downloaded from the NPRA website. Only one applicant and one local contact person, if any, should be named under Part 2 of the application form. All communications will be sent to the named applicant and the second contact person. For FIH clinical trials, applicants must provide additional information by completing the information provided in Appendix B3 of the application form.

4.4.4	**Receipt for processing fee,** if applicable Every CTIL application must be accompanied by a processing fee. The CTIL application processing fee is RM 500.00 per product, to be paid in Malaysian Ringgit (RM). Payment for the processing fee can be performed after screening, according to *Borang Penyerahan Yuran Pemprosesan*. The processing fee can be paid using a credit card, debit card, bank draft, money order, or postal order payable to 'Biro Pengawalan Farmaseutikal Kebangsaan'. Note: Foreign currencies are not acceptable. The processing fee is not refundable. CTX application is free of charge.
4.4.5	A copy of **Company Registration Certificate,** if applicable The company as defined in 4.1.2 must be registered with *Suruhanjaya Syarikat Malaysia*. In the case where a sponsor appoints the company, the sponsor must authorise the applicant from the company to be the holder of the CTIL/CTX. Refer to Section 4.4.6 for Letter of Authorisation. A copy of Company Registration Certificate is not required for an investigator-initiated trial.
4.4.6	**Letter of Authorisation**, if applicable Letter of Authorisation should be submitted in cases where; • Sponsor or a PI decides to use a service of a CRO for the conduct of a clinical trial, or; • The applicant is not the sponsor or product owner. In the case of an investigator-initiated trial involving "poison/drug", the letter of authorisation should be provided by the PI to the nominated applicant. A format of Letter of Authorisation in Appendix B1 may be used as a guide.
4.4.7	A copy of the applicant's **Poison Type A Licence** for pharmacists in the private sector, or **annual retention certificate (ARC)** for public pharmacists, whichever is applicable. For other applicant, a copy of the applicant's **Malaysia National Registration Identity Card** must be submitted.

4.4.8	A copy of **the opinion(s) of the EC** Following the directive issued by the DPS on *Keperluan Mendaftar Jawatankuasa Etika dengan Pihak Berkuasa Kawalan Dadah*, NPRA will only accept opinions issued by EC that is registered with the DCA. The applicant is advised to refer to the NPRA website for the current list of EC that is registered with the DCA. CTIL/CTX applications and EC applications may be submitted in parallel. The letter of favourable opinion of the EC, along with the attendance list, should be sent to NPRA as soon as possible once available.
4.4.9	**Clinical trial protocol** The updated version of a clinical trial protocol must be submitted. The version submitted should be the same version which has been submitted to the EC. The clinical trial protocol should be in the format provided in *Section 6, Malaysian Guideline for GCP* and must include the definition of the end of trial. For a bioequivalence (BE) study, the formula used with detailed stepwise calculation is required to justify the sample size needed. If a two-stage design is adopted in the study, a decision tree or a diagram, which depicts the methodology, must be stated in the study protocol. Implementation of the Decentralised Clinical Trial (DCT) and Digital Health Technology (DHT), if applicable, must be specified in the trial protocol.
4.4.10	**Declaration by investigator/PI** Original copy of declaration by investigator/PI of each trial site must be provided. A format of the document can be found in Appendix D2. Investigator protocol signature page will not be accepted.
4.4.11	**GCP certificate and CV for investigator/PI of each trial site** It is expected that the investigator/PI is qualified, has approved training in GCP, and has the experience to assume responsibility for the proper conduct of the trial. The GCP certificate and a brief CV of the investigator/PI of each trial site must be provided. • The GCP course should be approved by National Committee for Clinical Research (NCCR), Ministry of Health Malaysia. The requirement is in accordance with the current version of Malaysian Guideline for GCP. • For a BE study, the GCP certificate, CV and Declaration by the investigator at the clinical site must also be provided if the investigator is not the PI.
4.4.12	**Informed consent form (Initial version only for one of the trial sites)** The initial version of informed consent form (ICF) must be provided. The ICF must be in English or *Bahasa Melayu*.

4.4.13 **Pharmaceutical data for products that require CTIL/CTX**

Quality data should be submitted in a logical structure, such as the headings of the following appendices. The following appendices outline the pharmaceutical data format for different types of IP:

- Appendix D1: IP in Clinical Trials
- Appendix D2: Modified Registered Comparator Products in Clinical Trials
- Appendix D3: Generic Products in BE Studies
- Appendix D4: Placebo Products in Clinical Trials
- Appendix D5: Herbal Medicinal Products in Clinical Trials
- Appendix D6: Biological Products in Clinical Trials

Stability data

The applicant and the sponsor are responsible for ensuring that the products used are stable for the duration of the clinical trial.

The shelf life should be based on available stability data. Extrapolation may be used. An acceptable shelf life extension plan should be included in the pharmaceutical data, which comprises the following elements:

- specification against which the product is tested
- criteria used to extrapolate data
- analysis of trends
- proposed extension based on available real-time data and acceptable accelerated data – this should not exceed four times the available real-time data to a maximum of 12 months or 12 months plus the available real-time data, e.g.:

03 months real-time data	12 months shelf life
06 months real-time data	18 months shelf life
12 months real-time data	24 months shelf life
24 months real-time data	36 months shelf life

The same principles can be applied to biological and biotechnological products where an acceptable shelf life extension plan should comprise the following elements:

- Specifications against which the product is tested
- Proposed extension based on available real-time data.

A minimum of one (1) batch of stability studies under accelerated and real-time conditions for a minimum of 3 months should be provided.

Stability studies should be conducted in compliance with ASEAN/International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) stability guidelines. Stability data of the IP after reconstitution or dilution, if applicable, should be submitted to support the in-use period of the reconstituted or diluted IP.

For FIH clinical trials, a minimum of one (1) batch of stability studies under accelerated and real-time conditions for a minimum of 1 month should be provided.

BE studies

For BE studies, the test product should generally originate from a batch of at least 1/10 of the production scale or 100,000 units, whichever is higher, unless otherwise justified.

	Appendix D3, *Section 4.S Drug Substance* should be provided only for BE studies involving chemical entities that have not been registered in Malaysia. **IP being tested is DCA-registered product** In the case where the IP being tested is a DCA-registered product, the applicant may submit a declaration letter from the sponsor or the product owner in place of pharmaceutical data, certificate of analysis (CoA), and evidence of Good Manufacturing Practice (GMP) Compliance. The declaration letter should confirm that the quality of the IP being tested is the same as that of the DCA-registered product and include any differences (if any) and the impact of the difference on the quality.
4.4.14	**Label for all products that require CTIL/ CTX** The applicant must ensure that labels of products that require CTIL/CTX meet the labelling requirements, according to Appendix E. The particulars on the outer packaging of the IP, or where there is no outer packaging, on the immediate packaging, must appear in *Bahasa Melayu* or English.
4.4.15	**Evidence of Good Manufacturing Practice Compliance** Investigational products are required to be produced in accordance with the PIC/S *Annex 13, Guidelines of GMP for Medicinal Products*. A current copy of Certificate of GMP Compliance for the manufacturer of investigational product and final batch releaser only should be submitted. The name and address of the manufacturer stated in the application form and the GMP certificate must be identical. Any discrepancy in the information must be justified. The certificate must be valid at the time of submission. <u>Local manufacturer in Malaysia</u> A valid copy of *"Lesen Pengilang"* issued by NPRA must be submitted. For herbal products with therapeutic claims manufactured locally, the products should be manufactured at PIC/S GMP grade manufacturing facilities. <u>Manufacturer outside of Malaysia</u> (a) Certificate/ evidence of GMP compliance from PIC/S member countries must be provided. (b) If the document in (a) cannot be provided, Qualified Person's (QP) Declaration Equivalence to EU GMP for Investigational Medicinal Product (IMP) and proof of QP registration must be provided. (c) For ICH Regulatory Member Countries, a valid certificate or evidence of GMP compliance with the following information must be submitted: i. Name of Investigational Product (IP) manufacturer ii. Address of manufacturing site under inspection iii. Scope of Inspection iv. Dosage form covered during inspection v. Inspection date vi. Conclusion of the inspection vii. Validity Period of GMP Status viii. Official Stamp of the Issuing Authority <u>Manufacturer in ASEAN countries</u> A valid Certificate of GMP Compliance issued by National Drug Regulatory Authority

	(NDRA) as mutually agreed in ASEAN Sectoral Mutual Recognition Arrangement (MRA) for GMP Inspection of Manufacturers of Medicinal Products must be provided. Manufacturer which has been inspected by the United States Food and Drug Administration (US FDA) A document that shows the listing of the manufacturer in the US FDA Drug Establishments Current Registration Site must be submitted to fulfil the requirement of GMP compliance. **Note:** NPRA may request additional evidence of GMP compliance when necessary.
4.4.16	**Investigator's Brochure** For content and format of the investigator's brochure (IB), reference is made to *Section 7, Malaysian Guideline for GCP*. Unavailability of IB is generally acceptable for most BE studies. However, IB must be provided for a BE study involving a chemical entity which is not registered in Malaysia. Generally, toxicity studies are expected to be performed in compliance with Good Laboratory Practice (GLP).
4.4.17	**Overall risk and benefit assessment** This section should provide a brief integrated summary that critically analyses the non-clinical and clinical data in relation to the potential risks and benefits of the proposed trial unless this information is already provided in the protocol. In the latter case, the applicant should cross-refer to the relevant section in the protocol. The text should identify any studies that were terminated prematurely and discuss the reasons. The assessment is not mandatory for a BE study.
4.4.18	**A copy of scientific advice from other regulatory agencies, if available**
4.4.19	**Electronic format** All documents must be submitted in a CD/DVD-ROM electronic format. Refer to section 4.6.3 for preparation of the CD/DVD-ROM.
4.4.20	**Other or additional documents** Any other trial-related documents that could be relevant for the review of the clinical trial application by NPRA may be submitted, e.g. published clinical data, if applicable.

4.5 Additional requirements

4.5.1 General requirements

Guidelines/guidance issued by the ICH, EMA, and US FDA may serve as a guide in the development process of a pharmaceutical.

The CTIL/CTX holder must inform NPRA of any information that casts doubt on the continued validity of the data that has been submitted to NPRA.

NPRA may request further supplementary data and/or additional documents, including GLP certification and the GLP final report, for the application of CTIL/CTX, where necessary.

4.5.2 Non-modified, registered comparator/auxiliary product

If the comparator/auxiliary product used is a non-modified, registered comparator/auxiliary product sourced from other countries, an approved package insert or document equivalent to the package insert, e.g. summary of product characteristics, can be submitted as a supporting document in place of pharmaceutical data, certificate of analysis, certificate of GMP Compliance and investigator's brochure. The approved package insert provided should be from the country where the product is being sourced. The applicant must ensure that the manufacturer as stipulated in the package insert is the same as the manufacturer in the application form. Should the provided package insert not contain information on shelf life and storage condition, it will be sufficient to state the respective expiry date and storage condition assigned by the manufacturer.

4.5.3 Modified registered comparator/auxiliary product

For comparator/auxiliary product that will be modified (e.g. encapsulation, repackaging), Appendix D2 and certificate of GMP Compliance (as in 4.4.15) for the manufacturer involved in the modification should be provided. Approved package insert or document equivalent to the package insert, e.g. summary of product characteristics from the country where the product is sourced from, should be submitted. The applicant must ensure that the manufacturer as stipulated in the package insert is the same as the manufacturer in the application form.

4.5.4 Biosimilar product

Full quality dossier, which includes comparability exercise of physicochemical properties, biological activity, purity and impurities must be submitted at the level of active substance and medicinal product between the biosimilar product and reference medicinal product. Results from these studies should be reviewed from the point-of-view of the potential impact on efficacy and safety.

The nature and complexity of the reference medicinal product will have an impact on the extent of the nonclinical studies needed to confirm biosimilarity. In addition, any differences observed between the biosimilar and reference medicinal product in the physicochemical and biological analyses will also guide the planning of the nonclinical studies. Other factors that need to be taken into consideration include the mechanism(s) of action of the drug substance (for example, the receptor(s) involved) in all authorised indications of the reference medicinal product, and the pathogenic mechanisms involved in the disorders included in the therapeutic indications.

A stepwise approach should be applied during nonclinical development to evaluate the similarity of the biosimilar and its selected reference medicinal product. At first, in vitro studies should be conducted and then a decision made on whether or not additional in vivo animal studies are required.

Animal studies should be designed to maximize the information obtained. The 3Rs principles for animal experiments (Replace, Reduce, Refine) should always be followed to minimize the use of animals in testing. In cases where in vivo animal studies are required, they should be comparative in nature and should be designed to detect differences in response between the biosimilar and the reference medicinal product and not just the response per se. The in vivo animal studies should provide information on, including but not limited to, the PD effect and non-clinical toxicity (at least one repeat dose toxicity study). In some instances, combined PK/ PD studies may be done in order to provide useful information on the relationship between exposure and effect.

Comprehensive characterization and comparison showing similarity at the quality and nonclinical (in vitro) level are the basis for establishing comparability, with a tailored confirmatory clinical data package required as needed.

4.5.5 Vaccines

Generally, the applicant is expected to provide quality documents for vaccine products in the format specified in Appendix D6.

This guideline should be read in conjunction with other relevant guidelines by WHO, ICH, US FDA, EMA, and etc. These include, but are not limited to:

1. WHO Guidelines on nonclinical evaluation of vaccines, TRS No 927, Annex 1
2. WHO Guidelines on the non-clinical evaluation of vaccine adjuvants and adjuvanted vaccines, TRS No 987, Annex 2
3. WHO Guidelines on clinical evaluation of vaccines: regulatory expectations, TRS No 1004, Annex 9 (Replacement of Annex 1 of WHO Technical Report Series, No. 924)
4. European Medicines Agency (EMA). Guideline on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1) (EMA, London; 2023).
5. EMA Guideline on quality aspects included in the product information for vaccines for human use (EMA/CHMP/BWP/133540/2017)
6. USFDA Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product (January 1999)
7. WHO Guidelines on stability evaluation of vaccines, TRS No 962, Annex 3

4.5.6 Cell and Gene Therapy Products

Applications for CTIL/CTX is applicable for Cell and Gene Therapy Products (CGTPs) that fall under Class II. This guideline should be read in conjunction with Guidance Document and Guidelines for Registration of Cell and Gene Therapy Products (CGTPs) in Malaysia 2016.

The applicant may refer to EMA guidelines for the requirements of quality, non-clinical, and clinical data of investigational advanced therapy medicinal products in clinical trials, as well as other relevant laws and regulations.

For clinical trials involving stem cell and cell based therapies, recommendation from the National Committee in Ethics of Cell Research and Therapy (NCERT) must be sought before initiation of the study. Reference is made to the Circular No.: KKM87/P1/26/10Jld.18(41).

4.5.7 FIH Clinical Trials in Malaysia

First-in-human (FIH) trials start with the initial administration of a novel active ingredient into humans. Traditionally, FIH trials were most associated with a single ascending dose (SAD) design, which was subsequently followed by a multiple ascending dose (MAD) trials. Currently, the increasing practice is to perform FIH and early phase clinical trials with integrated protocols that combine a number of different study parts (e.g. SAD, MAD, and food effects). FIH includes trials with a dose higher than that previously tested in humans.

The CTIL/CTX application for FIH clinical trials will be accepted in stages. For FIH trials, the category of product(s) that will be accepted are new chemical entities, herbal products, and biologics (except CGTP). Reference is made to the DPS directives *(4) dlm. BPFK/PPP/07/25 Jld.3* and *NPRA.600-1/9/13(17)Jld.1*.

Clinical trials that involve generic products, biosimilar products, or registered herbal products with an indication for "traditionally used" when being tested at an approved dosage for therapeutic claims are not considered FIH trials.

In addition to the documents as required in Section 4.4, the following documents should be supplemented for CTIL/CTX applications involving FIH clinical trials:

4.5.7.1 **Evidence of Phase 1 Unit Accreditation by NPRA**

The Phase 1 Unit where the FIH trial is planned to be conducted must be listed on the NPRA Phase I Unit Accreditation Programme. Evidence of this listing must be submitted.

4.5.7.2 **Proof of insurance**

The insurance must include compensation policy of any damage suffered by a subject resulting from participation in a FIH clinical trial.

4.5.7.3 **Declaration by Sponsor in original format**

A format for Declaration by Sponsor can be found in Appendix B3.

Application for CTIL/CTX involving FIH clinical trial will only be tabled to the approval meeting for deliberation once the favourable opinion from EC is received.

4.5.8 Investigational products containing psychotropic substance or dangerous drug

For CTIL applications involving products containing psychotropic substances or dangerous drugs, the applicant must obtain Import Authorisation from the Pharmacy Enforcement Division, Ministry of Health Malaysia after obtaining CTIL. The applicant may contact the Pharmacy Enforcement Division for further information regarding the disposal and exportation of these IPs.

4.5.9 Investigational products manufactured solely for a clinical trial in a foreign country

As the investigational product is manufactured solely for a clinical trial conducted outside of Malaysia, documents as required in 4.4.8, 4.4.10, and 4.4.11 are exempted. The registration with NMRR is also not necessary.

4.6 Administrative requirements

4.6.1 Presentation

All data, including supplementary data, submitted in support of an application should be bound. Binders with durable covers containing A4 size paper, which can be dismantled and reassembled, are required. The external dimensions of the white 2-ring binders should be 290 x 370 mm and 80 mm in thickness. If more than one binder is needed, they should be clearly labelled as numbered volumes (e.g. 'volume 1/2', 'volume 2/2' etc).

The documents should be filed according to the sequence shown on the contents page in Appendix A, equipped with a tab file divider. The applicant is encouraged to print the entire document one page per sheet and double-sided.

4.6.2 Language

The application form must be filled out in English or *Bahasa Melayu*.

All data, including supplementary data, supportive documents, labels, and package inserts, must be in English *or Bahasa Melayu* and must be legible.

In cases where supportive documents are not originally in English or *Bahasa Melayu*, a copy of the document in its original language, accompanied by an authenticated translation in English or *Bahasa Melayu,* must be submitted.

4.6.3 CD/DVD-ROM document submission

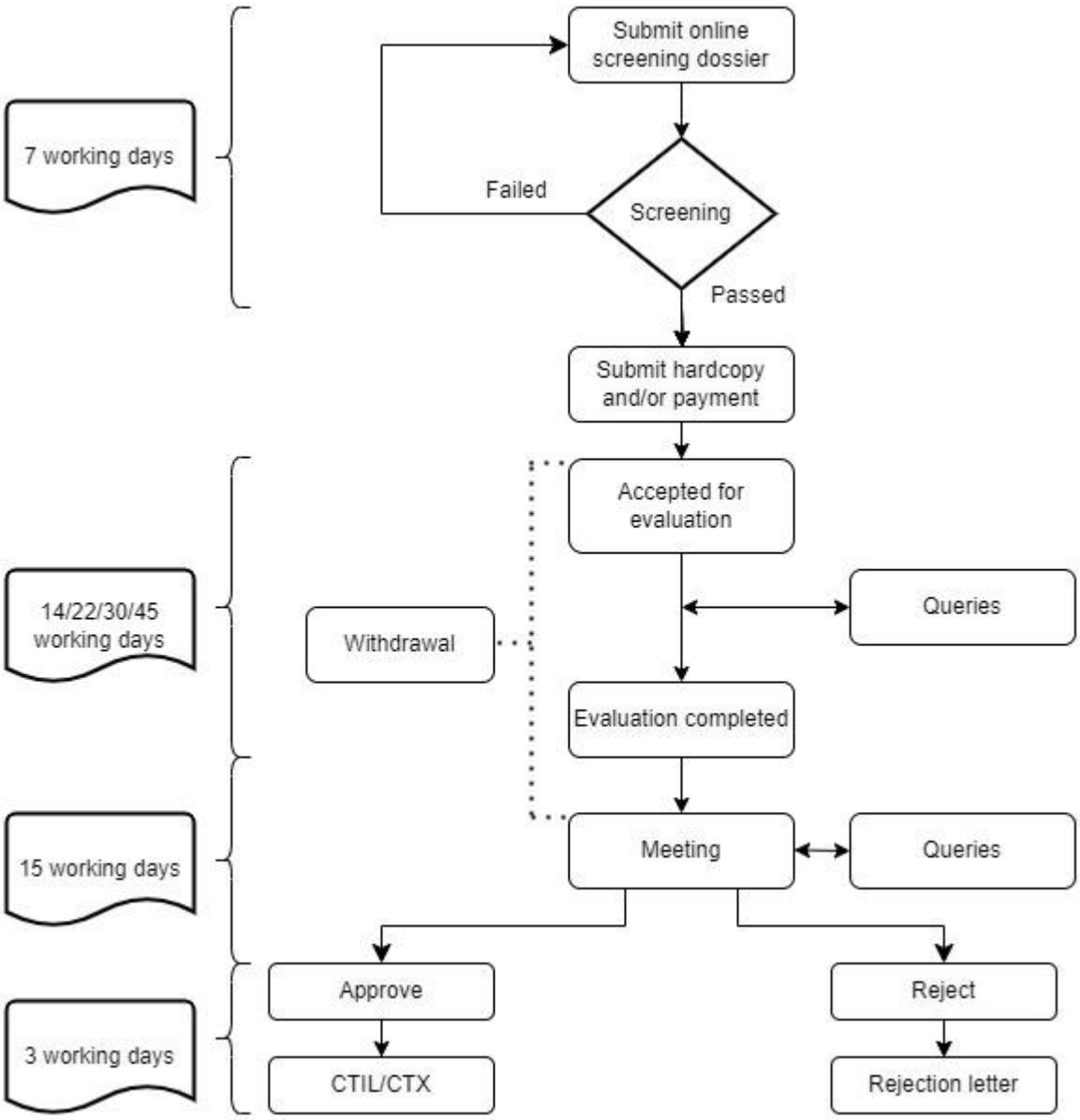
Electronic format of documents must be submitted in a CD-ROM in PDF format with searchable text except for the application form in the Word version, PDF files with searchable text can be created by all PDF tools from a source file in a text format (e.g. MS Word). If the only version of a document available is in paper, then scanning to PDF and Optical Character Recognition (OCR) routine should be undertaken to create searchable text. In the event the OCR routine is used, the applicant is responsible for ensuring the quality of the text created completely matches the original text. The applicant must not submit password-protected documents.

The envelope of the CD-ROM should be labelled clearly with the document title, version number and date. Should more than one CD-ROM be necessary, they should be clearly labelled as numbered volumes (e.g. 'volume 1/2', 'volume 2/2' etc.).

A standardised file organisation for CTIL/CTX electronic application dossier has been developed to improve clarity, consistency, and accessibility. Compliance with this structure ensures easy identification and access to necessary documents, enabling efficient evaluation and processing by NPRA. It also keeps all application material organised in a consistent manner. Prospective applicants can download the standardised file organisation from the NPRA website at this link: https://www.npra.gov.my/index.php/en/guideline-for-the-submission-of-product-samples-for-laboratory-testing/clinical-trial/clinical-trial-application-forms.html. All applicants must diligently prepare their electronic application files according to the prescribed format.

5 Processing of CTIL/CTX Application

5.1 Flow Chart: CTIL/CTX application process



5.2 Timelines

All CTIL/CTX application will be assessed within the following timeline:

- 45 working days for FIH clinical trials, clinical trials involving biological/biotechnological products, CGTPs as well as herbal products with therapeutic claim. For FIH clinical trials, this timeline includes the review time taken by external Panel of Expert(s).

- 30 workings days for all products except those products mentioned above.

With the exception of FIH clinical trials, fast-track reviews may be considered for applications of new IP for treatment or prevention during pandemic or epidemic situations in the interest of public health. Fast-track CTIL/CTX applications will be assessed within the following timeline:

- 22 working days for clinical trials involving biological/biotechnological products, CGTP products, and herbal products with therapeutic claim.

- 14 working days for all products except those products mentioned above.

For CTX applications, Day 0 is the day of receipt of a complete CTX application dossier. For CTIL applications, Day 0 is the day a complete CTIL application dossier AND the official receipt of payment is received. During the evaluation phase, the evaluator may have queries raised related to the application. The clock will stop on the day the query is e-mailed to the applicant. The clock will start when the response to all the queries is received. The number of query correspondence allowed is two (2) times.

The time taken by the applicant to address all evaluation queries should not exceed 30 working days, regardless of the number of correspondences. CTIL/CTX application may be rejected if NPRA does not receive a satisfactory response for the queries requested by the evaluator. Extension of more than 30 working days can only be applied with valid justification.

5.3 Withdrawals of Applications

An CTIL/CTX application can be withdrawn at any time before the application is tabled into the meeting for decision. A formal letter of withdrawal providing a brief explanation of the reasons should be provided. The processing fee is not refundable for withdrawn application.

6 Decisions of the NPRA/DCA

The applicant and second contact person, if available, will be notified via e-mail the result of the CTIL/CTX application.

The CTIL/CTX will be issued within three (3) working days after a decision has been made in the committee meeting and consented by the DPS.

For a rejected application, a rejection letter will be issued by DCA and sent directly to the applicant via post.

The DPS/DCA reserves the right to revoke the licence if the licensee does not comply with regulatory requirements as specified in the CDCR 1984 and other applicable guidelines and requirements.

7 Conditions for CTIL/CTX

The CTIL/CTX holder must submit the Country Level Drug Accountability Report [Appendix G1]. In addition, the CTX holder must submit the Manufacturing Drug Accountability Report [Appendix G2].

The product must only be supplied to the investigator(s) at the trial site(s) named in the application for the clinical trial import licence, for the purpose and use as stated in the said application. No change in trial site will be made without prior approval of NPRA.

The CTIL/CTX holder must be responsible in ensuring all Suspected Unexpected Serious Adverse Reactions (SUSARs) arisen from clinical trials conducted in Malaysia and other multicentre overseas are reported to NPRA:

- For fatal or life threatening SUSARs, the initial report should be submitted as soon as possible but no later than 7 calendar days and followed by a report as complete as possible within 8 additional calendar days.

- For non-fatal or non-life threatening SUSARs, the initial report should be reported as soon as possible but no later than 15 calendar days. Follow up information should be actively sought and submitted as it becomes available.

NPRA must be immediately informed after ethical approval, should there be any changes to the clinical trial protocol.

The CTIL/CTX holder must inform NPRA of any information that casts doubt on the continued validity of the data which has been submitted to NPRA.

The CTIL/CTX holder must ensure that the evidence of GMP compliance is valid throughout the period of validity of CTIL/CTX.

The CTIL/CTX holder must ensure that adequate precautions are taken for all study medication(s) such as storing study medication(s) in a securely locked cabinet, access to which is limited to prevent theft or illegal distribution.

The CTIL/CTX holder must inform NPRA immediately or within 15 working days of early termination of the clinical trial to which the licence/CTX relates and shall state the reason for the decision.

The CTIL/CTX holder should obtain a favourable opinion from the EC before initiation of the clinical trial at each site.

The DPS/DCA may, at any time, revoke CTIL/CTX and may amend the conditions to CTIL/CTX.

The CTIL/CTX is valid for 3 years from the date of issuance. Uncollected CTIL/CTX after 6 months of issuance will be cancelled unless otherwise justified.

The CTIL/CTX holder is responsible for the safekeeping of the CTIL/CTX and all the relevant approval letters. In case of loss of any of these documents, the holder is required to lodge in a police report immediately. The holder is required to write and inform NPRA regarding the loss of CTIL/CTX accompanied with a certified true copy of the police report. Should the CTIL/CTX be required for further importation/ manufacturing of IP, a certified true copy of the CTIL/CTX will be provided to the holder, upon request.

8 Withdrawal of CTIL/CTX Post Approval

In general, the applicant may withdraw the CTIL/CTX at any time.

The CTIL/CTX holder shall inform NPRA pertaining to the decision to withdraw the import licence of IP before the end of the validity of such licence and should state the reason(s) for the decision. The CTIL/CTX of the withdrawn product will become invalid and will be returned. A new application (Refer to 4.3) must be submitted if the IP is required again at a later date.

9 Reporting of Amendment/Update after CTIL/CTX Approval

9.1 Notification of amendment/update

The CTIL/CTX holder is responsible for notifying NPRA should there be any amendment or update to the clinical trial protocol, pharmaceutical data (including shelf life extension), IB and other related documents. For protocol amendment, NPRA must be notified after a favourable opinion from EC has been obtained for each site involved. For protocol with shared CTIL/CTX, updated IB or pharmaceutical data can be submitted in one cover letter mentioning all protocols involved.

The revised ICF is not required to be submitted to NPRA.

NPRA may request for further supplementary data or documentation when appropriate.

9.2 Administrative requirement

The notification of an amendment or update must be submitted in hardcopy and should include the following:

a) Signed cover letter, including in its subject line the NMRR Registration number with a description of the amendment.
b) Supporting information: The amendment to the clinical trial protocol, pharmaceutical data and/or IB must be submitted in a CD/DVD-ROM format. The applicant should refer to Section 4.6.3 for the preparation of the CD/DVD-ROM documents.

9.3 Change of sponsor

The applicant shall notify NPRA if there is any change of sponsor for the clinical trial. The following documents must be included in the notification:

a) A cover letter that includes the date of transfer of responsibilities.
b) A letter on a headed company paper from the current sponsor confirming the transfer of the study.
c) A letter on a headed company paper from the new sponsor confirming that they accept the role of sponsor for this study

Other company documents should not be submitted as part of this submission; e.g. protocol.

10 Guidance for the Application of Variation

All variation applications can only be submitted once the application of CTIL/CTX has been approved. Valid CTIL/CTX is required for all variation applications. Thus, the applicant should ensure the CTIL/CTX is valid throughout the whole study, i.e. until the last site closure in Malaysia, although there is no importation and manufacturing of IPs. The following documents should be included in every application of variation:

a) A cover letter, including with a description of the variation application.
b) Application form together with the relevant appendix in the form (NPRA/427/03).
c) A copy of valid CTIL/CTX for all the products involved in the clinical trial.
d) A copy of the latest Lampiran A issued for the protocol.

Each variation application (e.g. additional quantity of IP, change of CTIL/CTX holder, etc.) must be submitted as a separate application. Therefore, the applicant must include the

documents as stated above (a-d), for each variation application. Every application should be bound in a management file/ binder, where appropriate.

All variation applications will be assessed within 15 working days. Variation application may be rejected if NPRA does not receive satisfactory response for the queries or information requested by the evaluator after 15 working days. For variation application involving issuance of CTIL, the processing fee is not refundable.

The applicant and second contact person, if available, will be notified via e-mail of the result of the variation application. Approval letter/Lampiran A uncollected after 6 months of issuance will be cancelled unless otherwise justified.

The variation application will be processed after receiving documents as listed in the table below unless otherwise specified:

No.	Variation Application	Documents Required
10.1	Additional Quantity of IP	• Justification of additional quantity. Examples of justification for additional quantity of IP are treatment duration extension due to protocol amendment, additional trial subjects, to replace expired IP, etc. • Calculation of quantity • Information of previously approved quantity for IP • IP accountability, if applicable
10.2	Additional/Change of Trial Site (See Note 1)	• Original declaration by investigator/ PI of each trial site • GCP certificate for investigator/ PI of each trial site. • CV for investigator/ PI of each trial site • Information of previously approved quantity for IP, if applicable • EC approval, if available (See Note 5)
10.3	Change of CTIL/CTX Holder (See Note 2)	• Change of CTIL/CTX holder within the **same company** a. Reason for the change of CTIL/CTX holder b. Poison Licence Type A/ ARC of the new holder • Change of CTIL/CTX holder to a **different company** a. Reason for the change of CTIL/CTX holder b. Poison Licence Type A/ ARC of the new CTIL/CTX holder c. Company registration certificate of the new CTIL/CTX holder d. Letter of Authorisation for Transfer of CTIL/CTX Holder. A format of this letter in Appendix C1 may be used as a reference. e. Statement of Acceptance. Format for Statement of Acceptance can be found in Appendix C2.
10.4	Additional IP, e.g. • Different strength • Different dosage form • Different vial size	• Justification for additional IP • Calculation of quantity • Pharmaceutical data (See Note 3) • CoA

	• Different final volume • Auxiliary product • Comparator • Placebo	• IP Label • Evidence of GMP Compliance (refer to Section 4.4.15) • Official Receipt for processing fee (See Section 4.4.4) • Information of previously approved quantity for IP
10.5	Additional/ Change of Manufacturer	• Evidence of GMP Compliance (refer to Section 4.4.15)
10.6	CTIL/CTX Renewal (See Note 4)	• Official receipt for processing fee (See 4.4.4) • Information of previously approved quantity for investigational product
10.7	Change in the name and address of the applicant's company	• A copy of Company Registration Certificate • A copy of the applicant's Poison Licence Type A for pharmacist in the private sector or ARC for a public pharmacist, whichever applicable
10.8	Change of investigator/ PI	• Declaration by investigator/ PI(original copy) • GCP certificate for investigator/ PI • CV for investigator/ PI • EC approval, if available (See Note 5)
10.9	Other variation e.g Change in pack size/ type of packaging	• Justification of variation • Supporting document

Note 1: This application is not required for a clinical trial conducted in a foreign country.

Note 2: This application must be submitted by the initial CTIL/CTX holder.

Note 3: For additional IP involving additional strength, dosage form, vial size and final volume, only pharmaceutical data for the drug product is required. For additional IP due to other reasons, pharmaceutical data for both the drug substance and drug product is required. If the additional IP is a comparator, please refer to 4.5.2 and 4.5.3. This application is not applicable for an IP involving new active substance. For IP involving new active substance, it will be considered as a new CTIL/CTX application instead of variation application.

Note 4: The payment should be made for the CTIL to be renewed. However, separate CTIL/CTX renewal application should be made for each protocol sharing the same CTIL/CTX. Application for CTIL/CTX renewal can be made within 6 months before the CTIL/CTX expiration date. All successful applications will be granted a renewal period of 3 years. However, the start date of the renewed CTIL/CTX will depend on the completed document submitted based on the following scenarios:

- Complete application accepted between 1 and 6 months and BEFORE the expiration date. The start date of renewed CTIL/CTX will be continuous from the current CTIL/CTX.

- Complete application accepted within 1 month BEFORE the expiration date. The start date of renewed CTIL/CTX will be subjected to the date of approval, i.e. the date might not be continuing from the current CTIL/CTX.

- Complete application accepted within 3 months AFTER the expiration date. The application will only be accepted with a valid justification. Once accepted and later approved, the start date of renewed CTIL/CTX will be one working day after the date of approval.

- Complete application accepted AFTER 3 months from the expiration date will not be processed. The applicant is advised to submit it as a new CTIL/CTX application if necessary. (Refer to Section 4.3)

Note 5: EC approval letter should be submitted to NPRA as soon as possible once it is available. Parallel submission to NPRA and EC is allowed.

11 Safety Decision Arising from Report Analysis / Action taken by Other Regulatory Authority

The sponsor/ CTIL/CTX holder is required to inform NPRA within 48 hours of the occurrence of any new, significant safety events that may jeopardise the safety of the subjects, which have arisen from an analysis of overseas reports, or suspension/prohibition of a clinical trial concerning safety which has been taken by another country's regulatory agency.

The sponsor should inform all Malaysian investigator(s) and through the investigator, the EC, of this information.

The sponsor/ CTIL/CTX holder is also required to promptly provide clinical details of any individual overseas ADR reports if requested by NPRA.

The sponsor/ CTIL/CTX holder must notify the NPRA via email to the Head of Investigational Product Evaluation and Safety Section, followed by a hardcopy submission to NPRA.

12 Reporting of Suspected Unexpected Serious Adverse Reaction

Clinical safety information arising from clinical trials in which the IPs are authorised for use under CTIL/CTX must be reported to NPRA, particularly the SUSAR. Unless stated otherwise, reporting of safety information from clinical trials without CTIL/CTX (e.g., a Phase IV study that is mostly observational or non-interventional) is out of the scope of this guideline.

The SUSAR must be notified in accordance with ICH Guideline E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting and in the format of CIOMS form (Appendix H1: CIOMS Form). The applicant may refer to Appendix H2: Reporting Requirements and Timeline to NPRA and Appendix H3: Process of Qualifying SUSAR Reporting to NPRA when deciding upon the SUSAR report that should be reported to NPRA and the prescribed reporting timeline.

Other than SUSAR report, submission of safety information such as 6-monthly SUSAR line listing, annual safety report, development safety update report (DSUR), periodic safety update report (PSUR) etc. is currently not mandatory, but will be generally accepted.

12.1 When to Start and End Reporting

The reporting of SUSAR must commence on the date a notification of CTIL/CTX approval is received from NPRA. This activity must continue until the CTIL/CTX involved has expired or the End of Study Summary Reports have been submitted for all trial sites in Malaysia, whichever is later.

12.2 How to Report

The SUSAR reports should be submitted through email at the address provided below. All efforts should be made to send the reports electronically. In the event that the electronic submission infrastructure is unavailable (e.g., due to maintenance), the reports can be submitted in hardcopy. An acknowledgement of receipt will be made for all submissions received by NPRA.

Email: mysusar@npra.gov.my

The submission of SUSAR reports should be standardised as follows:

a) A cover letter (Appendix H4: Template of Cover Letter), either in email body or company letterhead.

b) Report(s) should be in PDF format.

c) Report(s) from the same clinical trial should be submitted with one cover letter.

d) Report(s) should be compiled but segregated into different files according to the source of the reports (local/foreign).

13 Interim Report

In cases of trials lasting for more than six months, an interim report must be submitted in hardcopy annually no later than one year after the initial approval date until end of trial. It is acceptable for a report to be submitted within the month that it is due. The interim report for all trial sites in Malaysia should be submitted in a single report. Please refer to Appendix F for the format of an Interim Report.

14 Protocol Deviation

All protocol deviation(s) related to inclusion or exclusion criteria, the conduct of the trial, patient management, or patient assessment and the corrective action/ preventive action taken, in Malaysia should be reported to NPRA at an interval determined by the holder. Such reports must be submitted no later than one year after the initial approval date and continue until end of trial. The CTIL/CTX holder is expected to follow the timeline specified for the interim report.

Any deviation(s) from the protocol that significantly affect the credibility of study data or subject safety must be reported to the NPRA immediately upon the sponsor's awareness.

To submit a protocol deviation, the following steps are required:

1. Include a cover letter on official company letterhead with each submission.
2. Attach a protocol deviation report to the email and rename it according to the reference number. The report should be in Excel format.
3. Refer to Form NPRA-433-07-1 on the NPRA's website for the submission format.
4. All correspondence related to protocol deviation should be sent to mygcp@npra.gov.my. Please note that hard copy will not be accepted.
5. If no protocol deviation occurs during the reporting interval, the applicant is not required to notify NPRA

15 End of Trial / Trial Discontinuation

15.1 End of trial

End of a clinical trial means the last visit of the last subject, or at a later point in time as defined in the protocol.

The CTIL/CTX holder must inform NPRA within 3 months from the last site closure in Malaysia. The applicant should refer 15.3 for the documents to be submitted at the end of trial.

15.2 Early trial termination/ Temporary halt

Early termination of a clinical trial means the premature end of a clinical trial due to any reason before the conditions specified in the protocol are complied with.

Temporary halt of a clinical trial means an interruption not provided in the protocol of the conduct of a clinical trial by the sponsor with the intention of the sponsor to resume it.

The CTIL/CTX holder must inform the NPRA within 15 working days of temporary halt or early termination of the clinical trial. The reasons should be clearly explained, and any follow-up measures taken for safety reasons should be described. Additionally, for early trial termination, CTIL/CTX holder must include documents to be submitted at the end of the trial (see 15.3).

15.3 Documents to be submitted at the end of the trial

15.3.1 End of Study Summary Report

The CTIL/CTX holder must submit to NPRA an End of Study Summary Report pertaining to the site conducting the trial within 3 months from the site closure. The report should be submitted for each trial site. The applicant should refer to Appendix F for the format of the report. Original CTIL/CTX, Lampiran A and variation approval documents will no longer be required to be returned to NPRA at the end of the trial.

15.3.2 Drug Accountability and Disposal Report

Drug Accountability and Disposal Report must be submitted to NPRA within 3 months from the last site closure in Malaysia unless otherwise justified. The report should include:

- Format for Country Level Drug Accountability Report can be found in Appendix G1
- Format for Manufacturing Drug Accountability Report can be found in Appendix G2
- For CTX, stability data and CoA for each batch manufactured

Disposal / Return of Unused IP

- Confirmation of the local drug disposal or return of unused drug supplies to the country of origin or regional depot.
- For local disposal, all IPs should be disposed of by the authorised bodies/authorities and documented. Disposal shall comply with the Environmental Quality Act 1974 and applicable regulations. Destruction documentation should be provided.

15.3.3 Clinical Study Report

NPRA must be informed of the trial findings. The report must be submitted within 1 year after the completion of the full trial or within 1 year from the frozen file or data lock date for international multicentre studies.

NPRA must be informed of any possible delay in the submission of the report, particularly where the delay is unavoidable as in multicentre studies.

The report should comply with ICH E3 Structure, and Content of Clinical Study Reports in CD/DVD-ROM format. The envelope of the CD/DVD-ROM should be printed with protocol number and table of contents (document title, version number and date).

16 Archiving

It is the responsibility of the investigator and the sponsor to archive safely all the documents related to the trial.

17 Inspection by NPRA

The objectives of the inspection are to ensure the rights, safety and well-being of study subjects are protected, to verify the validity of the data submitted to NPRA, to maintain the integrity of scientific testing, and to ensure compliance with the legislation/regulation, GCP principles and the Declaration of Helsinki (Appendix I). An inspection may be conducted by NPRA at the trial site, at the sponsor's and/ or CRO's facilities, or at other establishments deemed appropriate by NPRA. Failure to allow to do so may result in regulatory actions such as product registration being refused or de-registered, and the investigator/ trial site being disqualified, which includes delisting of the BE Centre and Phase 1 Unit from the existing NPRA compliance program.

18 Frequently Asked Questions (FAQ)

The applicant is encouraged to refer our FAQs on the Clinical Trials page, which addresses many common queries, prior to reaching out for assistance. The FAQs can be accessed at the links below:

https://www.npra.gov.my/index.php/en/component/sppagebuilder/911-faq-managing-clinical-trials-during-covid-19-in-malaysia-npra.html

https://www.npra.gov.my/index.php/en/clinical-trials-safety-reporting.html

SECTION II: GUIDELINES ON APPENDIX

INTRODUCTION

1. Section II comprises recommended formats for Appendix A until I.

2. Details of particulars and supporting documentation should be enclosed as specified.

   Failure to enclose necessary details and supporting documents may result in a delay in the processing, or rejection of an application.

3. Headings set out for each appendix are minimum general requirements. These may not be applicable in all circumstances; nor are they exhaustive.

   Interpretation of these guidelines should be flexible and related to the nature and proposed use of the product.

4. Where a heading is not applicable, or information is not available, indicate clearly in the appropriate sections.

5. Data in addition to those specified in the guidelines may be submitted to support the application for CTIL/CTX. Such data must be presented in a well-compiled manner, with a summary of the particulars.

These guidelines do not preclude any other information required by the NPRA. Such additional information must be supplied to the NPRA on request.

Appendix A: Table of Content

Folders	Subfolders	Description
1	1.1	Company cover letter
	1.2	Letter of authorisation
2	2.1	CTIL/CTX application form
	2.2	Receipt of processing fee
	2.3	Poison Type A Licence for pharmacist in private sector OR Annual Retention Certificate for public pharmacist OR Malaysia National Registration Identity Card
	2.4	Company Registration Certificate
	2.5	Phase 1 Unit Accreditation Certificate by NPRA (for First-in-Human study only)
3	3.1	Clinical trial protocol
	3.2	Overall risk and benefit assessment
	3.3	Informed consent form
	3.4	Investigator's Document (CV, GCP Certificate, Declaration by Investigator/ Principal Investigator)
	3.5	Opinion of Ethics Committee(s)
	3.6	Proof of Insurance Cover (for First-in-Human study only)
	3.7	Declaration by Sponsor for First-in-Human study
4	4.1	Pharmaceutical data for all products that require CTIL/ CTX
	4.2	Good Manufacturing Practice evidence
	4.3	Certificate of analysis of drug substance and drug product
	4.4	Label(s)
5	-	Investigator's brochure
6	6.1	Scientific advice from other regulatory agencies
	6.2	Others, please continue the listing and specify document name
7	7.1	Internal correspondence
	7.2	External correspondence
	7.3	Evaluation reports by IPESS
	7.4	Variation history and related documents
8	8.1	Interim reports
	8.2	End of Study Summary Report
	8.3	Drug Accountability and Disposal Report
	8.4	Clinical study report

Appendix B1: Format for Letter of Authorisation

SPONSOR Letterhead (registered address, e-mail and telephone)

LETTER OF AUTHORISATION

Date:

……,
(Sponsor's Name)

a company operating under the laws of …….., located in …… do hereby authorise

Local applicant company's name and address:
Tel no.:

to represent us in Malaysia for the application of the Clinical Trial Import Licence/ Clinical Trial Exemption for:-

Clinical Trial Title : …….
Protocol Number : …….

(Local applicant company's name) is authorised to be the Clinical Trial Import Licence / Clinical Trial Exemption holder and will be responsible for all matters pertaining to the Clinical Trial Import Licence/ Clinical Trial Exemption for the above-mentioned study protocol.

Thank you.

Sincerely,

(Signature)
**Full name & Title/ Position*
Company stamp

Appendix B2: Format for Declaration by Investigator/ Principal Investigator

Clinical Trial Title:

Protocol Number:

Name of Investigator/ Principal Investigator:

Name of the Trial Site:

A current brief Curriculum Vitae is attached.

1. I will fulfil the responsibilities of my role as an investigator/principal investigator in the above-mentioned clinical trial and comply with the Malaysian Guideline for Good Clinical Practice, legal, ethical as well as regulatory requirements of Malaysia.

2. I have received approved training in Good Clinical Practice.

3. I have read and understood the attached Protocol, Investigator's Brochure and supporting documentation, and I will comply with the procedures and requirements included in them.

4. I will not commence with this trial before written approval has been received from the National Pharmaceutical Regulatory Agency (NPRA) and the relevant Ethics Committee.

5. I will obtain informed consent from all participants, or if they are not legally competent, from their legal representatives, parents, or guardians.

6. I will ensure that every participant (and other involved people, such as relatives) will be treated in a dignified manner and with respect.

7. I DECLARE: I have no conflict of interest in terms of financial interests or personal relationships that may inappropriately influence my responsibilities and conduct of this trial.

   Initials:……..

8. I DECLARE: I have not previously been associated with any clinical study that has been terminated, or study-site that was closed, due to failure to comply with Malaysian Guideline for Good Clinical Practice.

   Initials:……..

9. I DECLARE: This study has indemnity/insurance that will provide cover for my activities in this clinical trial, as required in Malaysia.

   Initials:……..

10. Upon request by DCA/ NPRA, the investigator PI/ institution should make available for direct access to all requested trial-related records.

Investigator’s Signature:
NRIC/ Passport no.: Date:
Official Stamp:

Appendix B3: Format for Declaration by Sponsor Involving FIH Clinical Trials

Clinical Trial

Clinical Trial Title:

Protocol Number:

Name of Sponsor:

Name of Investigational Product(s):

1. I will fulfil the responsibilities of my role as a sponsor in the aforementioned clinical trial and comply with the Malaysian Guideline for Good Clinical Practice, legal, ethical and regulatory requirements of Malaysia, as well as all other applicable laws and their regulations.

2. I undertake to indemnify the Drug Control Authority (DCA) and National Pharmaceutical Regulatory Agency (NPRA) against all actions, claims or proceedings in respect to any loss, injury or death of any person that may arise out of or in connection with the aforementioned clinical trial.

3. I will evaluate the safety of the Investigational Product(s) (IPs) being tested or used in the aforementioned clinical trial on an ongoing basis and be fully responsible towards the safety of every subject that has been dosed with the IP(s) in the clinical trial.

4. I will ensure that the aforementioned clinical trial will not commence before written approvals have been received from NPRA/DCA and the ethics committee.

Sponsor's Signature: Date:

Name of Undersigned: Official Stamp:

Appendix C1: Format for Letter of Authorisation for Transfer of CTIL/CTX Holder

SPONSOR Letter Head (full address, email address, telephone and fax number)

Deputy Director
Centre of Product and Cosmetic Evaluation
National Pharmaceutical Regulatory Agency (NPRA),
Ministry of Health Malaysia,
Lot 36, Jalan Profesor Diraja Ungku Aziz,
46200 Petaling Jaya,
Selangor.
(Attention: Investigational Product Evaluation and Safety Section)

Dear Sir/ Madam,

LETTER OF AUTHORISATION FOR TRANSFER OF CLINICAL TRIAL IMPORT LICENCE (CTIL) / CLINICAL TRIAL EXEMPTION (CTX) HOLDER

The above subject matter is referred.

2. We, *Name of Sponsor,* the undersigned as the sponsor for the said clinical trial listed below:

Clinical Trial Title: ……
Protocol Number: ……..

	Name of Product(s)	**CTIL/ CTX No.**
i.	……	……..

hereby authorise *Company name with business registration number and full address of the proposed new CTIL/ CTX holder* to be the CTIL/ CTX holder and to act on our behalf and be responsible for all matters pertaining to the CTIL/ CTX of the aforementioned clinical trial.

3. Therefore, we hereby terminate the existing CTIL/ CTX holder *Company name with business registration number and full address of the existing CTIL/ CTX holder* for the aforementioned clinical trial effective on *date of termination.*

Thank you.

Sincerely,

(Signature)
**Full name & Title/ Position*
Company stamp

cc: *Company of the proposed new CTIL/ CTX holder*
Company of existing CTIL/ CTX holder
} *(A copy of LOA shall be sent to these companies by the Sponsor)*

Appendix C2: Statement of Acceptance

STATEMENT OF ACCEPTANCE AS
CLINICAL TRIAL IMPORT LICENCE HOLDER/CLINICAL TRIAL EXEMPTION

1. I hereby agree to be the Clinical Trial Import Licence (CTIL)/Clinical Trial Exemption (CTX) holder for the product involved and study protocol below:

   Clinical Trial Title: ……
   Protocol Number: …….

	Product's Name	**CTIL/CTX No.**
i	……..	……..

2. I hereby agree that I have the sole responsibility for all matters pertaining to the CTIL/CTX as stipulated in the *Malaysian Guideline for Application of Clinical Trial Import Licence and Clinical Trial Exemption*.

Signature	:
Full name	:
Identity Card Number	:
Telephone number	:
Fax Number	:
Date	:
Official Company Stamp	:

Note:
To be signed by the proposed new CTIL/ CTX holder

Appendix D: General Information for Pharmaceutical Data

A.1 General Considerations

For impurities in IPs, a justification that the product is safe for its intended use, considering the anticipated exposure of volunteers and patients, respectively, will be required.

When compiling the documentation, the difference between "analytical procedure" and "analytical method" should be kept in mind. The term "analytical procedure" is defined in ICH Q2(A) and refers to the way of performing the analysis. The term "analytical method" refers to the principles of the method used.

A.2 Adventitious Agents Safety Evaluation:

All materials of human or animal origin used in the manufacturing process of both the drug/active substance and drug/medicinal product, or such materials coming into contact with drug/active substance or drug/medicinal product during the manufacturing process, should be identified. Information assessing the risk with respect to potential contamination with adventitious agents of human or animal origin should be provided in this section.

TSE agents

Detailed information should be provided on the avoidance and control of transmissible spongiform encephalopathy (TSE) agents. This information can include, for example, certification and control of the production process, as appropriate for the material, process and agent.

The “Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products, EMEA/410/01”in its current version is to be applied.

Viral safety

Where applicable, information assessing the risk concerning potential viral contamination should be provided in this section. The risk of introducing viruses into the product, and the capacity of the manufacturing process to remove or inactivate viruses should be evaluated.

For biological investigational product, the documentation should comply with the requirements outlined in the EMA guideline on virus safety evaluation of biotechnological investigational medicinal products (EMEA/CHMP/BWP/398498/05).

Other adventitious agents

Detailed information regarding the other adventitious agents, such as bacteria, mycoplasma, and fungi, should be provided in appropriate sections within the core dossier.

A.3. Excipients

For novel excipients, information as indicated in section S should be provided in line with the respective clinical phase.

Appendix D1: Pharmaceutical Data Format for Investigational Products in Clinical Trials

S DRUG SUBSTANCE

S.1 General Information:

S.1.1 Nomenclature
Information concerning the nomenclature of the drug substance (e.g. proposed INN-name, pharmacopoeial name, chemical name (IUPAC, CAS-RN), laboratory code, other names or codes, if any) should be given.

S.1.2 Structure
The data available at the respective stage of clinical development should be presented. They should include the structural formula, molecular weight, chirality/stereochemistry as far as elucidated.

S.1.3 General Properties
A list of physicochemical and other relevant properties of the active substance should be provided, in particular physicochemical properties that could affect pharmacological or toxicological safety, such as solubilities, pKa, polymorphism, isomerism, log P, permeability etc.

S.2 Manufacture:

S.2.1 Manufacturer(s)
The name(s) and address(es) and responsibilities of all manufacturer(s), including contractors, and each proposed production site involved in manufacture and testing should be provided.

S.2.2 Description of Manufacturing Process and Process Controls
A brief summary of the synthesis process, a flow chart of the successive steps including, for each step, the starting materials, intermediates, solvents, catalysts and critical reagents used should be provided. Drug substance manufacturing process should be described in the pharmaceutical data to such extent, so it is understood how impurities are introduced in the process, and why the proposed control strategy is suitable. This will typically include a description of multiple chemical transformation steps. Any relevant process controls should be indicated. Where critical steps in the synthesis have been identified, a more detailed description may be appropriate. The stereochemical properties of starting materials should be discussed, where applicable. For substances which comply to the European Pharmacopoeia (Ph. Eur.), the Pharmacopoeia of an EU Member State, the United States Pharmacopoeia (USP) or the Japanese Pharmacopoeia (JP) reference to the monographs is acceptable, but the suitability of the referenced monograph to adequately control the quality of the active substance (impurity profile) should be discussed by submission of sufficient information on the manufacturing process of the active substance.

The production scale or range of batch sizes to be used in the clinical trial should be stated.

S.2.3 Control of Materials
Materials used in the manufacture of the drug substance (e.g. raw materials, starting materials, solvents, reagents, catalysts) should be listed together with a brief summary on the quality and control of any attributes anticipated to be critical, for example, where control is required to limit an impurity in the drug substance, e.g. chiral control, metal catalyst control or control of a precursor to a potential genotoxic impurity.

S.2.4 Control of Critical Steps and Intermediates
In case of critical steps in the synthesis, tests and acceptance criteria for their control should be briefly summarised.

S.2.5 Process Validation and/or Evaluation
Not applicable for drug substances to be used in clinical trials.

S.2.6. Manufacturing Process Development
It should be documented if the manufacturing process significantly differs from that used for the production of the batches used in the non-clinical studies. In this case, a flow chart of the manufacturing process used for the drug substance used in the non-clinical studies should be presented.

Significant changes in the manufacturing process, which may impact on quality, should be discussed (e.g. change of route of synthesis).

S.3 Characterisation:

S.3.1 Elucidation of Structure and other Characteristics
The structure of chemically defined substances should be established with suitable methodology; relevant data should be provided.

S.3.2 Impurities
The impurities, degradation products and residual solvents, deriving from the manufacturing process or starting materials relevant to the drug substance used for the clinical trial, should be discussed.

Discussion on (potential) mutagenic impurities according to ICH M7 should be provided (structure, origin, limit justification). The level of detail necessary depends on the phase of the clinical trial.

Absence of routine control for solvents/catalysts used in the manufacturing process should be justified.

S.4 Control of the Drug Substance:

S.4.1 Specification(s)
The specifications, the tests used as well as their acceptance criteria should be specified for the batch(es) of drug substance(s) used in the clinical trial. Tests for identity and assay are mandatory. Upper limits, taking safety considerations into account, should be set for the impurities. They may need to be reviewed and adjusted during further development. The limits should be supported by the impurity profiles of batches of active substance used in non-clinical and clinical studies

The microbiological quality for drug substances used in aseptically manufactured products should be specified.

For substances which comply with a monograph of the Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP, reference to the relevant monograph will be sufficient, provided its suitability to adequately control the quality of the active substance from the specific source has been demonstrated. The specification should, however, include acceptance criteria for any relevant residual solvent or catalyst.

Additional information for phase II and phase III clinical trials

Specifications and acceptance criteria set for the previous phase I or phase II trials should be reviewed and, where appropriate, adjusted to the current stage of development.

S.4.2 Analytical Procedures
The analytical methods used for the drug substance should be described for all tests included in the specification (e.g. reverse-phase-HPLC, potentiometric titration, head-space-GC-FID, etc.). It is not necessary to provide a detailed description of the analytical procedures (see definition of analytical methods vs analytical procedures in Appendix D, A.1 General Considerations)

Reference to the relevant monograph/pharmacopoeia for substances which comply with monograph/pharmacopoeia is acceptable.

4.3 Validation of Analytical Procedures
For phase I clinical trials, the suitability of the analytical methods used should be confirmed. The acceptance limits (e.g. acceptance limits for the determination of the content of impurities, where relevant) and the parameters (specificity, linearity, range, accuracy, precision, quantification and detection limit, as appropriate) for performing validation of the analytical methods should be presented in a tabulated form.

Additional Information for phase II and III clinical trials
The suitability of the analytical methods used should be demonstrated. A tabulated summary of the results of the validation carried out should be provided (e.g. results or values found for specificity, linearity, range, accuracy, precision, quantification and detection limit, as appropriate). It is not necessary to provide a full validation report.

For substances which comply with a monograph of the Ph. Eur., the pharmacopoeia of an EU country, USP or JP, reference to the relevant monograph will be sufficient.

In case of major changes in analytical methods, cross-validation data should be presented especially for specified unknown impurities identified by their relative retention time (RRT) unless otherwise justified. A re-analysis of preclinical batch with the new method should also be considered, where relevant.

S.4.4 Batch Analyses
Batch results in a tabulated form or certificates of analysis for batches used in the current clinical trial, in the non-clinical studies and, where applicable, for representative batches used in previous clinical trials (e.g. in case the comparable quality of batches manufactured by previous processes has to be demonstrated), should be supplied. If these data are not available for the batches to be used in the current clinical trial, data for representative batches may be submitted instead.

The batch number, batch size, manufacturing site, manufacturing date, control methods, acceptance criteria and the test results should be listed.

The manufacturing process used for each batch should be assigned as stated under S.2.2 of this chapter.

S.4.5 Justification of Specification(s)
For substances for which reference to a pharmacopoeial monograph listed under S.4.1 of this chapter cannot be made, a brief justification of the specifications and acceptance criteria for impurities and any other parameters which may be relevant to the performance of the drug product should be provided based on safety and toxicity data, as well as the methods used for the control of impurities. The solvents and catalysts used in the synthesis should be taken into consideration.

S.5 Reference Standards or Materials:
The parameters characterising the batch of drug substance established as reference standard should be presented, where applicable.

S.6 Container Closure System:
The immediate packaging material used for the drug substance should be stated. If non-compendial materials are used, the description and specifications should be provided.

S.7 Stability:
The stability data available at the respective stage of development should be summarised in tables. Stability data should be provided for batch(es) manufactured according to the representative process (the same/very similar synthesis, comparable batch size). They can be supported by data from batch(es) manufactured by previous processes. The parameters known to be critical for the stability of the drug substance need to be presented, i.e. chemical and physical sensitivity, e.g. photosensitivity, hygroscopicity. Potential degradation pathways should be described. Alternatively, for active substances covered by a pharmacopoeial monograph, confirmation that the active substance will meet specifications at time of use will be acceptable.

The re-test period should be defined based on the available stability data and should be clearly stated. For drug substances covered by a Certificate of Suitability (CEP) which does not include a re-test date, supporting stability data and a re-test period should be provided. In case no re-test period is defined, a statement should be included that the drug substance is tested immediately before the drug product manufacture.

The re-test period can be extended without a substantial modification submission, if a stability protocol, re-test period extension plan and a statement that in case of any significant negative trend the Sponsor will inform the competent authority are provided. The stability protocol should cover the maximum planned re-test period.

P INVESTIGATIONAL PRODUCT UNDER TEST

P.1 Description and Composition of the Investigational Medicinal Product:
The qualitative and quantitative composition of the IP should be stated. For proprietary prefabricated components (e.g. capsule shells), flavours and excipient mixtures (e.g. film-coating mixtures), a qualitative composition is sufficient. A short statement or a tabulation of the dosage form and the function of each excipient should be included.

P.2 Pharmaceutical Development:
A short description of formulation development, including justification of any new pharmaceutical form or excipient, should be provided.

For early development, there may be no or only limited information to include in this section.

Where applicable, the compatibility with solvents used for reconstitution, diluents and admixtures should be demonstrated. For products to be reconstituted or diluted prior to their use, the method of preparation should be summarised and reference made to a full description in the clinical protocol or associated handling instructions which will be available at the clinical site should be provided.

Additional information for phase II and phase III clinical trials
If changes in the formulation or dosage form compared to the IP used in earlier clinical trials have been made, the relevance of the earlier material compared to the product under testing

should be described. Special consideration should be given to dosage form specific changes in quality parameters with potential clinical relevance, e.g. in vitro dissolution rate.

P2.1 Manufacturing Process Development
Changes in the current manufacturing process compared to the one used in phase I and phase II clinical trials, respectively, are to be explained. Special consideration should be given to dosage form specific changes in quality parameters with potential clinical relevance, e.g. in vitro dissolution rate.

P.3 Manufacture:

P.3.1 Manufacturer(s)
The name(s) and address(es) and responsibilities of all manufacturer(s), including contractors, and each proposed production site involved in manufacture and testing should be provided. In case that multiple manufacturers contribute to the manufacture of the IP, their respective responsibilities need to be clearly stated.

P.3.2 Batch Formula
The batch formula for the batch to be used for the clinical trial should be presented. Where relevant, an appropriate range of batch sizes may be given.

P.3.3 Description of Manufacturing Process and Process Controls
A flow chart of the successive steps, indicating the components used for each step and including any relevant in-process controls, should be provided. Also, a brief narrative description of the manufacturing process should be included.

Non-standard manufacturing processes or new technologies and new packaging processes should be described in more detail (EMA Annex II to Note for Guidance on Process Validation: Non-Standard Processes (CPMP/QWP/2054/03) can be referred).

P.3.4 Controls of Critical Steps and Intermediates
Information is not required for phase I and II clinical trials, except for
• non-standard manufacturing processes
• manufacturing processes for sterile products

For sterilisation by filtration, the maximum acceptable bioburden prior to the filtration must be stated in the application. In most situations, NMT 10 CFU/100 ml will be acceptable, depending on the volume to be filtered in relation to the diameter of the filter. If this requirement is not met, a pre-filtration through a bacteria-retaining filter should be carried out in order to obtain a sufficiently low bioburden. If the availability of the formulated medicinal product is limited, a prefiltration/filtration volume of less than 100 ml may be tested if justified.

A statement that aseptic processing operations were validated using media fill runs should be provided.

Additional information for phase III clinical trials
If critical manufacturing steps have been identified; their control, as well as possible intermediates, should be documented.

Should intermediates be stored, assurance should be provided that duration and conditions of storage are appropriately controlled.

P.3.5 Process Validation and/or Evaluation
Data are not required during the development phases, i.e. clinical phases I to III, except for non-standard sterilisation processes not described in the pharmacopoeias and non-standard

manufacturing processes. In these cases, the critical manufacturing steps, the validation of the manufacturing process as well as the applied in-process controls, should be described.

P.4 Control of Excipients:

P.4.1 Specifications
Reference to pharmacopoeias should be indicated. A certificate of analysis should be provided for excipients used, which is a non-compendial excipient.

For excipients not described in one of the mentioned pharmacopoeias, reference to the relevant food chemical regulations (e.g. FCC) can be made. For excipient mixtures composed of pharmacopoeial substances, e.g. pre-fabricated dry mix for film- coating, a general specification of the mixture will suffice. For excipients not covered by any of the afore-mentioned standards, an in-house monograph should be provided. Specification for capsule shells should be provided.

P.4.2 Analytical Procedures
Reference to pharmacopoeias should be indicated. In cases where reference to a pharmacopoeial monograph listed under P.4.1 of this chapter cannot be made, the non-compendial analytical methods used should be mentioned.

P.4.3 Validation of the Analytical Procedures
Not applicable.

P.4.4 Justification of Specifications
Not applicable.

P.4.5 Excipients of Animal or Human Origin
Refer to Appendix D A.2.

P.4.6 Novel Excipients
For novel excipients, details are to be given on their manufacturing process, characterisation and control in relevance to product safety. Information on, e.g. their manufacturing process, characterisation and stability are to be included.

P.5 Control of the Investigational Medicinal Product:

P.5.1 Specifications
The chosen release and shelf-life specifications should be submitted, including test methods and acceptance criteria. A minimum test on identity, assay and degradation products should be included for any pharmaceutical form.

Upper limits may be set for both individual degradation products and the sum of degradation products. Safety considerations should be taken into account; the limits should be supported by the impurity profiles of batches of active substance used in non-clinical/clinical studies. The specifications and acceptance criteria should be reviewed and adjusted during further development.

Drug product specific tests and acceptance criteria should be included in the specifications in line with the pharmaceutical form used (e.g. dissolution/disintegration for oral solid dosage forms; uniformity of dosage units; or pH, bacterial endotoxins and sterility for parenteral dosage forms). The omission of drug product specific tests should be justified.

For radiopharmaceuticals, it should be specified which tests are carried out prior to batch release and which tests are carried out retrospectively. For kits for radiopharmaceutical preparations, appropriate tests after radioactive radio-labelling should be stated.

For medicinal products to be reconstituted or diluted prior to their use, the acceptable quality standard after preparation should be stated and documented by development testing.

Additional information for phase II and phase III clinical trials
Specifications and acceptance criteria set for the previous phase I or phase II trials should be reviewed and, where appropriate, adjusted to the current stage of development.

P.5.2 Analytical Procedures
The analytical methods should be described for all tests included in the specification (e.g. dissolution test method).

For complex or innovative pharmaceutical forms, a higher level of detail may be required.

P.5.3 Validation of Analytical Procedures
For phase I clinical trials, the suitability of the analytical methods used should be confirmed. The acceptance limits (e.g. acceptance limits for the determination of the content of impurities, where relevant) and the parameters (specificity, linearity, range, accuracy, precision, quantification and detection limit, as appropriate) for performing validation of the analytical methods should be presented in a tabulated form.

Additional information for phase II and III clinical trials
The suitability of the analytical methods used should be demonstrated. A tabulated summary of the results of the validation should be provided (e.g. results or values found for specificity, linearity, range, accuracy, precision, quantification and detection limit, as appropriate). It is not necessary to provide a full validation report.

P.5.4 Batch Analyses
Batch results in a tabulated form and certificates of analysis for representative batches (same manufacturing site, same manufacturing process, same composition, and comparable batch size, unless otherwise justified,) to be used in the clinical trial should be provided. The results should cover the relevant strengths to be used in the trial.

Results or certificates of analysis for batches representative for the IP to be used in the clinical trial should be provided.

The batch number, batch size, manufacturing site, manufacturing date, control methods, acceptance criteria and the test results should be listed.

Results for batches controlled according to previous, wider specifications are acceptable if the results comply with the specifications for the planned clinical trial.

P.5.5 Characterisation of Impurities
Additional impurities/degradants observed in the IP, which was not covered by section S.3.2 of this chapter, should be stated.

P.5.6 Justification of Specification(s)
For IPs in phase I clinical trials, it will be sufficient to briefly justify the specifications and acceptance criteria for degradation products and any other parameters that may be relevant to the performance of the drug product. The toxicological justification should be given, where appropriate.

Additional information for phase II and phase III clinical trials
The choice of specifications and acceptance criteria for parameters which may affect efficacy or safety should be briefly justified.

P.6 Reference Standards or Materials:
The parameters for the characterisation of the reference standard should be submitted, where applicable. For radiopharmaceuticals, information should be provided on radioactive standards used in the calibration of radioactivity measurement equipment.

Section S.5 of this chapter - Reference Standards or Materials - may be referred to, where applicable.

P.7 Container Closure System:
The intended immediate packaging and additionally, where relevant, for the quality of the drug product, the outer packaging to be used for the IP in the clinical trial, should be stated. Where appropriate, reference should be made to the relevant pharmacopoeial monograph. If the product is packed in a non-standard administration device, or if non-compendial materials are used, description and specifications should be provided. For dosage forms that have a higher potential for interaction between filling and container closure system (e.g. parenterals, ophthalmic products, oral solutions), more details may be needed for phase III studies (e.g. extractables, leachables). For dosage forms where interaction is unlikely, e.g. solid oral dosage forms, a justification for not providing any information may suffice.

P.8 Stability:
The shelf-life of the IP should be defined based on the stability profile of the active substance and the available data on the IP. Minimum of 1 batch of stability studies under accelerated and real-time conditions for a minimum of 3 months should be provided.

Extrapolation may be used, provided that stability studies are conducted in parallel to the clinical studies and throughout its entire duration. This should include the proposal for the shelf-life extension, defining the criteria based on which the sponsor will extend the shelf-life during an on-going study. A stability commitment should be provided. Furthermore, bracketing and matrixing designs of appropriate IPs may be acceptable, where justified. The batches of drug product must meet specification requirements throughout the period of use. If issues arise, the applicant shall inform the NPRA of the situation, including any corrective action proposed.

Any proposal for a future shelf life extension should be stated. Stability protocol, shelf life extension plan and a statement that in case of any significant negative trend the Sponsor will inform the NPRA should be provided. The stability protocol should cover the maximum planned shelf life.

For preparations intended for applications after reconstitution, dilution or mixing, and products in multi-dose containers, excluding oral solid dosage forms, in-use stability data should be presented. In-use stability studies should cover the practice described in the clinical protocol. Relevant parameters should be monitored within the in-use stability studies (e.g. appearance, assay, impurities, visible and sub-visible particles, microbial contamination). Shelf life and storage conditions after first opening and/or after reconstitution and/or dilution should be defined. These studies are not required if the preparation is to be used immediately after opening or reconstitution and if it can be justified that no negative influence on the quality of the preparation through instabilities is to be expected.

Additional information for FIH Clinical Trial
For FIH Clinical Trial, it should be confirmed that an on-going stability program will be carried out with the relevant batch(es) and, before the start of the clinical trial, at least 1-month

stability data under accelerated and long-term storage conditions is available. The results from these studies should be summarised in a tabulated form. Supportive data from development studies should be summarised in a tabular overview. An evaluation of the available data and justification of the proposed shelf-life to be assigned to the IP in the clinical study should be provided.

Additional information for other phases of clinical trials

The available stability data should be presented in a tabulated form. An evaluation of the available data and justification of the proposed shelf-life to be assigned to the IP in the clinical study should be provided. Data should include results from studies under accelerated and long-term storage conditions. Minimum of 1 batch of stability studies under accelerated and real-time conditions for a minimum of 3 months should be provided.

Appendix D2: Pharmaceutical Data Format for Modified Registered Comparator Products in Clinical Trials

In preparing supplies for clinical trials, applicants often modify or process products which have already been registered in order to use them as comparator products in blinded studies.

As the product registration holder (PRH) of a comparator product is only responsible for the unchanged product in its designated and registered packaging, there is a need to ensure that the quality of the product is not negatively affected by the modifications performed by the applicant or sponsor of the clinical trial, with particular emphasis on the biopharmaceutical properties.

P MODIFIED COMPARATOR PRODUCT

P.1 Description and Composition:
In the case of any modification of the registered product other than repackaging, the complete quantitative composition of the preparation should be specified. All additional substances/materials added to the registered product should be listed with reference to pharmacopoeial or in-house monographs.

P.2 Pharmaceutical Development:
The modifications carried out on the registered comparator product should be described, and their influence on the quality of the product discussed. Special focus should be assigned to all parameters relevant for the function, stability and efficacy of the medicinal product, such as in-vitro dissolution and pH-value. It should be demonstrated that these parameters remain comparable to those of the unmodified product.

Compatibility with other solvents (that are not stated in the original SmPC) used for drug product reconstitution and dilution should be demonstrated. Compatibility studies reflecting the practice described in the clinical protocol (e.g. dispersion of a tablet or content of the hard capsule in water/juice/food) should be performed in case of unstable products and/or in case of preparation in advance.

In the case of solid oral dosage forms, comparative dissolution profiles of both original and modified comparator products should be provided to ensure unchanged bio-pharmaceutical properties. In those cases, where comparability cannot be established in vitro, additional clinical data to support equivalence may be necessary.

P.3 Manufacture:

P.3.1 Manufacturer(s) related to the Modification
The name(s) and address(es) and responsibilities of all manufacturer(s), including contractors, and each proposed production site involved in the modification, packaging/assembly and testing of the modified product should be provided. In case that multiple manufacturers contribute to the manufacture of the IP, their respective responsibilities need to be clearly stated.

P.3.2 Batch Formula
The batch formula for the batch intended to be used during the clinical trial should be presented. This does not apply to registered products which are only repackaged.

P.3.3 Description of Manufacturing Process and Process Controls

All steps of the modification of the registered medicinal product should be described, including in-process controls that are carried out. For details, reference is made to Appendix D1 section P.3.3.

P.4 Control of Excipients:

P.4.1 Specifications
Reference to pharmacopoeias should be indicated. A certificate of analysis should be provided for excipients used, which is non-compendial excipient.

For excipients not described in pharmacopoeias, reference to the relevant food-chemical regulations (e.g. FCC) can be made. For excipient mixtures composed of pharmacopoeial substances, e.g. pre-fabricated dry mix for film-coating, a general specification of the mixture will suffice. For excipients not covered by any of the afore-mentioned standards, an in-house monograph should be provided. Specification for capsule shells should be provided.

P.4.2 Analytical Procedures
In cases where reference to a pharmacopoeial monograph listed under P.4.1 of this chapter cannot be made, the analytical methods used should be indicated.

P.4.3 Validation of Analytical Procedures
Not applicable.

P.4.4 Justification of Specifications
Not applicable.

P.4.5 Excipients of Animal or Human Origin
Refer to Appendix D A.2.

P.5 Control of the Modified Comparator Product:

P.5.1 Specifications
The chosen release and shelf-life specifications of the modified comparator product should be submitted, including test methods and acceptance criteria. Generally, they should include description and identification of the drug substance as well as the control of important pharmaceutical and technological properties, such as dissolution. Where an intact solid oral dosage form that is easily identifiable by its colour, shape and marking is encapsulated, identification of the active substance may not be necessary, and visual examination may suffice for identification. Depending on the degree of modification of the registered product, additional quality criteria, e.g. determination of the drug substance(s) and impurities/degradants, may need to be specified and tested.

P.5.2 Analytical Procedures
For parameters relevant to the performance of the comparator product, e.g. dissolution, the methods should be described.

P.5.3 Validation of Analytical Procedures
The suitability of the analytical methods used should be demonstrated. A tabulated summary of the results of validation of the analytical methods should be provided (e.g. results or values found for specificity, linearity, range, accuracy, precision, quantification and detection limit, as appropriate). It is not necessary to provide a full validation report.

P.5.4 Batch Analyses
Results and certificates of analysis for the batch of modified comparator product to be used in the clinical trial or of a representative batch should be provided.

The batch number, batch size, manufacturing site, manufacturing date, control methods, acceptance criteria and the test results should be listed.

In case of more than one bulk manufacturing sites, it is necessary to provide results for batches which have been produced by each of the bulk manufacturing sites relevant for the current trial unless otherwise justified, (e.g. where one legal entity has multiple sites (in the same country), then batch analysis data from one site only would be sufficient).

P.5.5 Characterisation of Impurities
In those cases, where the comparator product has undergone significant modification by the sponsor, e.g. has been processed with an excipient hitherto not present in the formulation with a likely impact on product stability, and the original product is not known to be stable under normal conditions, special emphasis should be given to demonstrating that the impurity profile has not changed compared to the original product. For stable comparator products, where a small degree of modification has been undertaken by the sponsor, e.g. where an intact tablet is encapsulated using the ingredients already present in the tablet, justification for not quantifying impurities will suffice

This is not required for registered products which are only repackaged.

(Note: For the definition of "stable", refer ICH Q1A (R2) Stability Testing of New Drug Substances and Products, section 2.2.7 "Storage conditions").

P.5.6 Justification of Specification(s)
A justification of specification(s) will only be required in cases where a significant modification of the registered comparator product may affect the product's performance or safety.

P.6 Container Closure System:
The type of immediate packaging, material and package size(s) should be specified. If materials other than those registered are used, description and specifications should be provided. Where appropriate, reference should be made to the relevant pharmacopoeia monograph.

If the test/comparator product is packed in a non-standard administration device, or if non-compendial materials are used, a description and specifications should be provided.

P.7 Stability:
The applicant or sponsor of the clinical trial has to ensure that the modified comparator product is stable for at least the anticipated duration of the clinical trial in which it will be used.

In the case of a significant modification, e.g. grinding of a tablet, re-lubrication and compression, or processing with an excipient hitherto not present in the formulation with a likely impact on product stability, a minimum of stability data on the modified comparator product should be available, before the start of the clinical trial to allow an assessment of the impact of the modifications on product safety and stability.

A minimum of 1 batch of stability studies under accelerated and real-time conditions for a minimum of 3 months should be provided. The available stability data should be presented in a tabulated form. An evaluation of the available data and justification of the proposed shelf-life to be assigned to the IP in the clinical trial should be provided. Any degree of extrapolation may not exceed the shelf-life initially assigned to the specific batch of the registered product by its PRH.

In the case of only minor modifications, a justification of the stability over the intended study period may be acceptable.

In-use stability studies should be performed in case of use of the comparator product in different conditions as those described in the SPC (according to the clinical protocol), if not otherwise justified.

Appendix D3: Pharmaceutical Data Format for Investigational Products Containing Generics in Bioequivalence Studies

Appendix D3 describes the pharmaceutical data required for the test product.

S DRUG SUBSTANCE

S.1 General information:

S.1.1 Nomenclature
Information concerning the nomenclature of the drug substance (e.g. (proposed) INN-name, pharmacopoeial name, chemical name, code, other names, if any) should be given.

S.1.2 Structure
The structural formula should be presented.

S.1.3 General Properties
The main physicochemical and other relevant properties of the drug substance should be indicated.

S.2 Manufacture:

S.2.1 Manufacturer(s)
The name(s) and address(es) and responsibilities of all manufacturer(s), including contractors, and each proposed production site involved in manufacture and testing should be provided.

S.2.2 Description of Manufacturing Process and Process Controls
A brief summary of the synthesis process, a flow chart of the successive steps including, for each step, the starting materials, intermediates, solvents, catalysts and reagents used should be provided. The stereochemical properties of starting materials should be discussed, where applicable.

S.3 Characterisation:

S.3.1 Impurities
Impurities, possible degradation products and residual solvents deriving from the manufacturing process or starting materials relevant to the drug substance used for the bioequivalence study should be stated.

Discussion on (potential) mutagenic impurities should be provided (structure, origin, limit justification), if relevant.

Absence of routine control for solvents/catalysts used in the manufacturing process should be justified.

S.4 Control of the Drug Substance:

S.4.1 Specifications
The microbiological quality of drug substances used in aseptically manufactured products should be specified.

For substances which comply with a monograph of the Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP, no further details are required, provided its suitability to

adequately control the quality of the active substance from the specific source has been demonstrated. The specification should, however, include acceptance criteria for any relevant residual solvents and catalysts.

In cases where reference to a pharmacopoeial monograph listed above cannot be made, specifications, tests used as well as the acceptance criteria should be provided for the batch(es) of the drug substance(s) intended for use in the bio-equivalence study. Tests for identity and assay are mandatory. Upper limits, taking safety considerations into account, should be set for the impurities.

Where specifications are set for (potential) mutagenic impurities, the guidance given in relevant guidelines should be taken into consideration.

S.4.2 Analytical Procedures
For substances for which reference to a pharmacopoeial monograph listed under S.4.1 of this chapter cannot be made, the analytical methods used for the drug substance (e.g. reverse-phase-HPLC, potentiometric titration, head-space-GC, etc.) should be provided. However, a reference to pharmacopoeia for substances which comply with pharmacopoeia is accepted. It is not necessary to provide a detailed description of the analytical procedures (see definition of analytical methods vs analytical procedures in Appendix D A.1 General Considerations).

S.4.3 Validation of Analytical Procedures
For substances for which reference to a pharmacopoeial monograph listed under S.4.1 of this chapter cannot be made, the suitability of the analytical methods used should be demonstrated. A tabulated summary of the results of validation of the analytical methods should be provided (e.g. values found for repeatability, the limit of quantification, etc.). It is not necessary to provide a full validation report.

S.4.4 Batch Analyses
Certificates of analyses or batch analysis data for the batch(es) intended for use in the planned bioequivalence study or, in their absence, for representative batches, should be supplied. The batch number, batch size, manufacturing site, manufacturing date, control methods, acceptance criteria and test results should be listed.

S.4.5 Justification of Specifications
A brief justification of the specifications and acceptance criteria for impurities and any other parameters which may be relevant to the performance of the drug product should be provided based on safety and toxicity data, as well as the methods used for the control of impurities. The solvents and catalysts used in the synthesis should be taken into consideration.

S.5 Reference Standards or Materials:
The parameters characterising the batch of drug substance established as reference standards should be presented.

S.6 Container Closure System:
The immediate packaging material used for the drug substance should be stated.

If non-compendial materials are used, a description and specifications should be provided.

S.7 Stability:
The available stability data should be provided in a tabulated form. Alternatively, confirmation that the active substance will meet specifications at the time of use will be acceptable.

The retest period should be defined based on the available stability data and should be clearly stated. For drug substances covered by a Certificate of Suitability (CEP) which does not include a retest date, supporting stability data and a retest period should be provided. In case no retest period is defined, statement should be included that the drug substance is tested immediately before the drug product manufacture.

P INVESTIGATIONAL PRODUCT UNDER TEST

P.1 Description and Composition:
The qualitative and quantitative composition of the IP should be stated.

For proprietary prefabricated components (e.g. capsule shells), flavours and excipient mixtures (e.g. film-coating mixtures), a qualitative composition is sufficient. Standard terminology from the EDQM standard terms database should be preferably used for dosage forms, where applicable.

P.2 Pharmaceutical Development:
A brief narrative description of the dosage form should be provided.

P.3 Manufacture:

P.3.1 Manufacturer(s)
The name(s) and address(es) and responsibilities of all manufacturer(s), including contractors, and each proposed production site involved in manufacture, packaging/assembly and testing should be provided. In case multiple manufacturers contribute to the manufacture of the IP, their respective responsibilities in the manufacturing chain should be clearly indicated.

P.3.2 Batch Formula
The batch formula for the batch to be used in the planned bio-equivalence study should be presented. Where relevant, an appropriate range of batch sizes may be given.

P.3.3 Description of Manufacturing Process and Process Controls
A flow chart of the successive steps, including the components used for each step and including any relevant in-process controls, should be provided. Also, a brief narrative description of the manufacturing process should be included.

P.3.4 Control of Critical Steps and Intermediates
If critical manufacturing steps have been identified; their control, as well as possible intermediates, should be documented.

Should intermediates be stored, assurance should be provided that duration and conditions of storage are appropriately controlled.

P.3.5 Process Validation and/or Evaluation
Data are not required, except for non-standard sterilisation processes not described in the pharmacopoeia and non-standard manufacturing processes. In these cases, the critical manufacturing steps, the validation of the manufacturing process as well as the applied in-process controls, should be described.

P.4 Control of Excipients:

P.4.1 Specifications
Reference to pharmacopoeias should be indicated. An in-house monograph should be provided for excipients not covered by pharmacopoeias.

For excipient mixtures composed of pharmacopoeial substances, e.g. pre-fabricated dry mix for film-coating, a general specification of the mixture will suffice.

Specification for capsule shells should be provided.

P.4.2 Analytical Procedures
Reference to pharmacopoeias should be indicated. In cases where reference to a pharmacopoeial monograph listed under P.4.1 of this chapter cannot be made, the non-compendial analytical methods used should be mentioned.

P.4.3 Validation of Analytical Procedures
Not applicable.

P.4.4 Justification of Specifications
Not applicable.

P.4.5 Excipients of Animal or Human Origin
Refer to Appendix D A.2.

P.4.6 Novel Excipients
For novel excipients, details are to be given on their manufacturing process, characterisation and control in relevance to product safety. Information on, e.g. their manufacturing process, characterisation and stability are to be included.

P.5 Control of the Investigational Medicinal Product:

P.5.1 Specifications
The chosen release and shelf-life specifications should be submitted, including test methods and acceptance criteria.

At least, tests on identity, assay and degradation products should be included for any pharmaceutical form. Drug product specific tests defined in the Ph.Eur. monographs for dosage forms and acceptance criteria should be included in the specifications in line with the pharmaceutical form used (e.g. dissolution/disintegration for oral solid dosage forms; uniformity of dosage units; or pH, bacterial endotoxins and sterility for parenteral dosage forms). The omission of drug product specific tests should be justified.

P.5.2 Analytical Procedures
The analytical methods should be described for all tests included in the specification (e.g. dissolution test method).

For complex or innovative pharmaceutical forms, a higher level of detail may be required.

P.5.3 Validation of Analytical Procedures
The suitability of the analytical methods used should be demonstrated. A tabulated summary of the validation results should be provided (e.g. results or values found for specificity, linearity, range, accuracy, precision, quantification and detection limit, as appropriate). It is not necessary to provide a full validation report.

P.5.4 Batch Analyses
Certificates of analysis and batch analysis data for the batch(es) intended to be used in the planned bioequivalence study or, in their absence, representative batches, should be provided.

The batch number, batch size, manufacturing site, manufacturing date, control methods, acceptance criteria and the test results should be listed.

P.5.5 Characterisation of Impurities
Additional impurities/degradants observed in the IMP, but not covered by section S.3.1 of this chapter, should be stated.

P.5.6 Justification of Specification(s)
It will be sufficient to briefly justify the specifications and acceptance criteria for degradation products and any other parameters that may be relevant to the performance of the drug product. A toxicological justification should be given, where appropriate.

P.6 Reference Standards or Materials:
The parameters for the characterisation of the reference standard should be submitted, if no compendial reference standard is available.

Refer to Section S.5 of this chapter - Reference Standards or Materials, where applicable.

P.7 Container Closure System:
The intended immediate packaging and additionally, where relevant for the quality of the drug product, the outer packaging to be used for the IMP in the clinical trial, should be stated. Where appropriate, reference should be made to the relevant pharmacopoeial monograph. If the product is packed in a non-standard administration device, or if non-compendial materials are used, description and specifications should be provided. For dosage forms that have a higher potential for interaction between filling and container closure system (e.g. parenterals, ophthalmic products, oral solutions), more details may be needed. For dosage forms where interaction is unlikely, e.g. solid oral dosage forms, a justification for not providing any information may suffice.

P.8 Stability:
A minimum of 1 batch of stability studies under accelerated and real-time conditions for a minimum of 3 months should be provided.

Supporting data from development studies should also be summarised in a tabular overview. An evaluation of the available data and justification of the proposed shelf-life to be assigned to the IMP in the bioequivalence study should be provided. Extrapolation may be used, provided a commitment is included to perform an on-going stability study in parallel to the bioequivalence study.

Appendix D4: Pharmaceutical Data Format for Placebo Products in Clinical Trials

The quality documentation to be submitted for placebos is limited to the following sections of the product part.

P PLACEBO PRODUCT IN CLINICAL TRIALS

P.1 Description and Composition:
The qualitative and quantitative composition of the placebo should be stated. A short statement or a tabulation of the dosage form and the function of each excipient should be included.

For proprietary prefabricated components (e.g. capsule shells), flavours and excipient mixtures (e.g. film-coating mixtures), a qualitative composition is sufficient.

P.2 Pharmaceutical Development:
It should describe how possible differences of the placebo preparation in relation to the investigational medicinal product regarding taste, appearance and smell are masked, where applicable.

P.3 Manufacture:

P.3.1 Manufacturer(s)
The name(s) and address(es) and responsibilities of all manufacturer(s), including contractors, and each proposed production site and facility involved in manufacture and testing should be provided. In case that multiple manufacturers contribute to the manufacture of the placebo, their respective responsibilities need to be clearly stated.

P.3.2 Batch Formula
The batch formula for the batch to be used for the clinical trial should be presented. Where relevant, an appropriate range of batch sizes may be given.

P.3.3 Description of Manufacturing Process and Process Controls
A flow chart of the successive steps, indicating the components used for each step and including in-process controls should be provided. In addition, a brief narrative description of the manufacturing process should be included.

P.3.4 Control of Critical Steps and Intermediates
Information is not required except for manufacturing processes for sterile products.

P.3.5 Process Validation and/or Evaluation
Data are not required, except for non-standard sterilisation processes not described in the pharmacopoeia. In these cases, the critical manufacturing steps, the validation of the manufacturing process as well as the applied in-process controls, should be described.

P.4 Control of Excipients:

P.4.1 Specifications
Reference to pharmacopoeias should be indicated. A certificate of analysis should be provided for excipients used, which is non-compendial excipient.

P.4.2 Analytical Procedures
Reference to pharmacopoeias should be indicated. In cases where reference to a pharmacopoeial monograph listed under P.4.1 of this chapter cannot be made, the non-compendial analytical methods used should be reported.

P.4.3 Validation of Analytical Procedures
Not applicable.

P.4.4 Justification of Specifications
Not applicable.

P.4.5 Excipients of Animal or Human Origin
Refer to Appendix D A.2.

P.4.6 Novel Excipients
For novel excipients, details are to be given on their manufacturing process, characterisation and control in relevance to product safety. Information on, e.g. their manufacturing process, characterisation and stability are to be included. If the same novel excipient is already described in the pharmaceutical data for the respective test product, cross-reference to the relevant section will suffice.

P.5 Control of the Placebo Product:

P.5.1 Specifications
The chosen release and shelf-life specifications should be submitted, including test methods and acceptance criteria. The specifications should at a minimum include a test which enables to differentiate between the respective investigational medicinal product and the placebo.

P.5.2 Analytical Procedures
The analytical methods should be described for all tests included in the specification.

P.5.3 Batch Analyses
Results and certificates of analysis for the batch of placebo to be used in the clinical trial or of a representative batch should be provided.

The batch number, batch size, manufacturing site, manufacturing date, control methods, acceptance criteria and the test results should be listed.

P.6 Container Closure System:
The intended immediate packaging and additionally, where relevant for the quality of the drug product, the outer packaging to be used for the placebo in the clinical trial, should be stated.

P.7 Stability:
The shelf life of the placebo product should preferably cover the anticipated duration of the clinical trial. Stability studies are only required in cases where there is reason to suspect that the placebo product will undergo changes in its physical characteristics or degradation, respectively, e.g. microbial purity of multi-dose containers, hardness or appearance. In all other cases, a short justification of the assigned shelf-life will suffice.

Appendix D5: Pharmaceutical Data Format for Herbal Medicinal Products in Clinical Trials

Note: This is the recommended format for clinical trials involving herbal medicinal products with therapeutic claims. Spacing should be adjusted by the applicant where necessary. Extension sheets for details and supporting documents should be numbered and referenced appropriately.

1. Raw materials

1.1 Description

- Common or usual names of the plant, including:
  - Synonyms
  - The family name / the genus name
  - Parts of the plant

- Active Constituent(s)
  - Name of Active Constituent(s)
    (e.g.: those can be used as a characteristic profile for identification and quality control)

1.2 Authentication of the medicinal plants/ ingredients

- 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)

2. Active Substance(s) /Standardised Extract(s)

2.1 Description (Physical Characteristics)

- *For Example:*
  The extract is standardised to contain:
  - X% of compound A (assayed by, e.g. HPLC, UV Spectrophotometry etc.)
  - Y% of compound B (assayed by, e.g. HPLC, UV Spectrophotometry etc.)

2.2 Characterisation

- Characterisation profile is required in later phase clinical trials such as Phase 3 and Phase 4. For Active Substance(s) / Standardised Extract(s), details should be provided on the physical and phytochemical characterisation. Where applicable, details should be given on the biological activity.

2.3 Manufacturing of Active Substance(s) / Standardised Extract(s)

- Name and address and responsibilities of all manufacturer(s)

- Manufacturing Process
  - Brief description and principles
  - A flow chart of the successive steps indicating the components used for each step and including any relevant in-process controls

3. Finished Product

3.1 Description (Physical Characteristics)

3.2 Composition (Complete Formula)
- Active Ingredient(s)/ Standardised Extract(s)
  - Name of Active Ingredient(s)/ Standardised Extract(s)
- Other Ingredient(s), e.g. adjuncts, excipients, preservative, colour, flavour, etc.
  - Name of other ingredient(s)
- Packing/Pack Size (brief)

4. Manufacture of Finished Product

4.1 Name and address and responsibilities of all manufacturer(s), including contractors, and each proposed production sites involved in manufacture and testing

4.2 Complete Batch Manufacturing Master Formula
- Name of Ingredients (Active and otherwise)

4.3 Manufacturing Process
- Brief Description and Principles
  A summary of the manufacturing process and a flow chart of the successive steps, starting with the plant cultivation or the plant collection, should be provided. The in-process controls carried out should be documented. The main production steps should be indicated.
- A flow chart of the successive steps indicating the components used for each step and including any relevant in-process controls

5. Quality Control

5.1 State whether quality control is done in part or solely by the manufacturer's own quality control department or an external laboratory.

5.2 If quality control tests are done by an external laboratory, state
- Name and address of the laboratory
- Tests that are done by the external laboratory
- Reasons why the tests are not done by the manufacturer

5.3 Specifications of the Active Substance(s) / Standardised Extract(s)
- CoA for Active Substance(s) / Standardised Extract(s) need to be attached (**minimum of 1 batch**).

Test/Criteria	Acceptance Limits/Specifications	Methodology (Manufacturers etc.)
▪ Appearance		
▪ Qualitative Assay: o Identification/ Chemical fingerprint		
▪ Quantitative Assay for Active Constituents		

Test/Criteria	Acceptance Limits/Specifications	Methodology (Manufacturers etc.)
▪ Water content / Loss on drying		
▪ Microbial limits o Total bacterial count o Total yeast and mould o Bile tolerant gram-negative bacteria		
▪ Specific Pathogens o *Salmonella* spp. o *Escherichia coli* o *Staphylococcus aureus* o *Pseudomonas aeruginosa*		
▪ Heavy metal limits o Arsenic o Mercury o Lead o Cadmium		
▪ Extractive values* o Water Soluble o Ethanol Soluble		
▪ Impurities o Related/degraded substance o Pesticide residues o Solvent residues*		
▪ Adventitious Toxins* o Aflatoxins		

**Required only for Phase 3 & Phase 4*

5.1 Method of Identification of Marker Compounds in the Active Substance(s) / Standardised Extract(s)

5.2 Method of Analysis of Marker Compounds in the Active Substance(s) / Standardised Extract(s)

- Both of the method used for identification and analysis need to be explained.

5.3 Specifications of the Finished Products

- CoA must be certified by the Quality Assurance Manager. CoA for the recent batch should be submitted (**minimum of 1 batch**).
- Tests and Specification Limits (Check and Release Specifications)

Test/Criteria	Acceptance Limits/Specifications	Methodology (Manufacturers etc.)
▪ Appearance (e.g. capsules/tablets)		
▪ Qualitative Assay: o Chemical fingerprint		
▪ Quantitative Assay for Active Constituents		
▪ Water content / Loss on		

Test/Criteria	Acceptance Limits/Specifications	Methodology (Manufacturers etc.)
drying		
▪ Uniformity of Weight		
▪ Disintegration/Dissolution test		
▪ Microbial limits o Total bacterial count o Total yeast and mould o Bile tolerant gram-negative bacteria		
▪ Specific Pathogens o *Salmonella* spp. o *Escherichia coli* o *Staphylococcus aureus* o *Pseudomonas aeruginosa*		
▪ Heavy metal limits o Arsenic o Mercury o Lead o Cadmium		
▪ Extractive values* o Water Soluble o Ethanol Soluble		
▪ Impurities o Related/degraded substance o Pesticide residues o Solvent residues*		
▪ Adventitious Toxins* o Aflatoxins		

**Required only for Phase 3 & Phase 4*

6. Stability of Product

6.1 Storage condition

- Description of storage condition.

6.2 Proposed shelf life.

- If the extension of shelf life for clinical trial materials is required, the industry will provide supportive data to support the extension of shelf life. Supporting data in the form of re-test results will be considered.

6.3 Stability Studies

- Completed stability studies/ accelerated stability studies (summary of stability studies, characteristic and degradation products monitored, results and conclusions of completed stability studies).
- Stability studies results of at least one batch for a minimum duration of 3 months stability data under accelerated and long-term storage conditions are required.
- For early phase trials (e.g. Phase 1 & 2), at least 1-month stability data under accelerated and long-term storage conditions is required at the point of CTIL/CTX submission.

6.4 Outline of on-going or proposed stability studies.

6.5 Stability studies must be carried out in accordance to ASEAN/ ICH Stability Studies Guidelines.

7. Containers/ Packaging

Is there any known interaction between the product and packaging material? [Yes/No]

7.1 Immediate containers/ packaging
- Type
- Material
- Capacity, where applicable
- Closure and liner (type and material), where applicable

7.2 Other container(s)/ packaging(s)

7.3 Dose-measuring device/ applicators/ administration set/ etc., if any
- Description/ Type
- Material
- Capacity, where applicable

7.4 Packaging inclusions (desiccant, filler, etc.), if any
- Description and compositions

8. Labelling

8.1 Please refer to Appendix E.

8.2 Samples/proposed drafts of the following are required to be submitted:
- Label(s) for immediate package/container of product.
- Label(s) for outer package/container of product.
- Original Package insert(s) for comparator product.

Appendix D6: Pharmaceutical Data Format for Biological Investigational Products in Clinical Trials

S ACTIVE SUBSTANCE

S.1. General information

S.1.1. Nomenclature
Information concerning the nomenclature of the active substance (e.g. proposed INN-name, pharmacopoeial name, proprietary name, company code, other names or codes, if any) should be given.

S.1.2. Structure
A brief description of the predicted structure should be provided. Higher-order structure, schematic amino acid sequence indicating glycosylation sites or other post-translational modifications and relative molecular mass should be included, as appropriate.

S.1.3. General properties
A list of physicochemical and other relevant properties of the active substance should be provided including biological activity (i.e. the specific ability or capacity of a product to achieve a defined biological effect). The proposed mechanism of action should be discussed.

S.2. Manufacture

S.2.1. Manufacturer(s)
The name(s) and address(es) and responsibilities of each manufacturer, including contractors, and each proposed production site or facility involved in the manufacture, testing and batch release should be provided.

S.2.2. Description of the manufacturing process and process controls
The manufacturing process and process controls should be adequately described. The manufacturing process typically starts with a vial(s) of the cell bank and includes cell culture, harvest(s), purification, modification reactions and filling. Storage and shipping conditions should be outlined.

A flow chart of all successive steps including relevant process parameters and in-process-testing should be given. The control strategy should focus on safety relevant in-process controls (IPCs) and acceptance criteria for critical steps (e.g. ranges for process parameters of steps involved in virus removal) should be established for manufacture of phase I/II material. These in-process controls (process parameters and in process testing as defined in ICH Q11) should be provided with action limits or preliminary acceptance criteria. For other IPCs, monitoring might be appropriate and acceptance criteria or action limits do not need to be provided. Since early development control limits are normally based on a limited number of development batches, they are inherently preliminary. During development, as additional process knowledge is gained, further details of IPCs should be provided and acceptance criteria reviewed.

Batch(es) and scale should be defined, including information on any pooling of harvests or intermediates.

Any reprocessing during the manufacture of the active substance (e.g. filter integrity test failure) should be described and justified. Reprocessing could be considered in exceptional circumstances. For biological products, these situations are usually restricted to certain re-

filtration and re-concentration steps upon technical failure of equipment or mechanical breakdown of a chromatography column.

S.2.3. Controls of materials

Raw and starting materials
Materials used in the manufacture of the active substance (e.g. raw materials, starting materials, cell culture media, growth factors, column resins, solvents, reagents) should be listed identifying where each material is used in the process. Reference to quality standards (e.g. compendial monographs or manufacturer's in-house specifications) should be made. Information on the quality and control of non-compendial materials should be provided. Information demonstrating that materials (including biologically-sourced materials, e.g. media components, monoclonal antibodies, enzymes) meet standards applicable for their intended use should be provided, as appropriate.

For all raw materials of biological origin (including those used in the cell bank generation), the source and the respective stage of the manufacturing process where the material is used should be indicated. Summaries of safety information on adventitious agents for these materials should be provided in Appendix D, A.2.

Source, history and generation of the cell-substrate
A brief description of the source and generation (flow chart of the successive steps) of the cell-substrate, analysis of the expression vector used to genetically modify the cells and incorporated in the parental / host cell used to develop the Master Cell Bank (MCB), and the strategy by which the expression of the relevant gene is promoted and controlled in production should be provided, following the principles of ICH Q5D.

Cell bank system, characterisation and testing
A MCB should be established before the initiation of phase I trials. It is acknowledged that a Working Cell Bank (WCB) may not always be established.

Information on the generation, qualification and storage of the cell banks is required. The MCB and/or WCB should be characterised, and results of tests performed should be provided. Clonality of the cell banks should be addressed for mammalian cell lines. The generation and characterisation of the cell banks should be performed in accordance with the principles of ICH Q5D.

Cell banks should be characterised for relevant phenotypic and genotypic markers so that the identity, viability, and purity of cells used for the production are ensured.

The nucleic acid sequence of the expression cassette, including the sequence of the coding region, should be confirmed before the initiation of clinical trials.

As for any process change, the introduction of a WCB may potentially impact the quality profile of the active substance and comparability should be considered (see section S.2.6. Manufacturing process development).

The safety assessment for adventitious agents and qualification of the cell banks used for the production of the active substance should be provided in Appendix D, A.2 if appropriate.

Cell substrate stability
Any available data on cell-substrate stability should be provided.

S.2.4. Control of critical steps and intermediates

Tests and acceptance criteria for the control of critical steps in the manufacturing process should be provided. It is acknowledged that due to limited data at an early stage of development (phase I/II), complete information may not be available. Hold times and storage conditions for process intermediates should be justified and supported by data, if relevant.

S.2.5. Process validation
Process validation data should be collected throughout the development, although they are not required to be submitted.

For manufacturing steps intended to remove or inactivate viral contaminants, the relevant information should be provided in Appendix D, A.2, Adventitious agents safety evaluation.

S.2.6. Manufacturing process development

Process improvement
Manufacturing processes and their control strategies are continuously being improved and optimised, especially during the development phase and early phases of clinical trials. Changes to the manufacturing process and controls should be summarized, and the rationale for changes should be presented. This description should allow a clear identification of the process versions used to produce each batch used in non-clinical and clinical studies, in order to establish an appropriate link between pre-change and post-change batches. Comparative flow charts and/or list of process changes may be used to present the process evolution. If process changes are made to steps involved in viral clearance, justification should be provided as to whether a new viral clearance study is required, or whether the previous study is still applicable.

Comparability exercise
Depending on the consequences of the change introduced and the stage of development, a comparability exercise may be necessary to demonstrate that the change would not adversely impact the quality of the active substance. In early phases the main purpose of this exercise is to provide assurance that the post-change product is suitable for the forthcoming clinical trials and that it will not raise any concern regarding the safety of the patients included in the clinical trial.

This comparability exercise should typically follow a stepwise approach, including a comparison of quality attributes of the active substance and relevant intermediates, using suitable analytical methods. Analytical methods usually include routine tests and may be supplemented by additional characterisation tests (including orthogonal methods), as appropriate. Where the manufacturer's accumulated experience and other relevant information are not sufficient to assess the risk introduced by the change, or if a potential risk to the patients is anticipated, a comparability exercise based only on quality considerations may not be sufficient.

During early phases of non-clinical and clinical studies, comparability testing is generally not as extensive as for an approved product. In the case of a first-in-human clinical trial, an IP representative of the material used in non-clinical studies should be used (see Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07)).

S.3. Characterisation

S.3.1. Elucidation of structure and other characteristics
Characterisation of a biotechnological or biological substance (which includes the determination of physicochemical properties, biological activity, immunochemical properties, purity and impurities) by appropriate techniques is necessary to allow a relevant specification

to be established. Reference to the literature data only is not acceptable. Adequate characterisation is performed in the development phase before phase I and, where necessary, following significant process changes.

All relevant information available on the primary, secondary and higher-order structure including post-translational (e.g. glycoforms) and other modifications of the active substance should be provided.

Details should be provided on the biological activity (i.e. the specific ability or capacity of a product to achieve a defined biological effect). Usually, prior to initiation of phase I studies, the biological activity should be determined using an appropriate, reliable and qualified method. Lack of such an assay should be justified. It is recognised that the extent of characterisation data will increase during development.

The rationale for selection of the methods used for characterisation should be provided, and their suitability should be justified.

S.3.2. Impurities

Process related impurities (e.g. host cell proteins, host cell DNA, media residues, column leachables) and product-related impurities (e.g. precursors, cleaved forms, degradation products, aggregates) should be addressed. Quantitative information on impurities should be provided, including maximum amount for the highest clinical dose. For certain process-related impurities (e.g. antifoam agents), an estimation of clearance may be justified.

In case only qualitative data are provided for certain impurities, this should be justified.

S.4. Control of the active substance

When process validation data are incomplete, the quality attributes used to control the active substance are important to demonstrate pharmaceutical quality, product consistency and comparability after process changes. Therefore the quality attributes controlled throughout the development process should not be limited to the tests included in the specification for which preliminary acceptance criteria have been set.

S.4.1. Specification

The specification for the batch(es) of the active substance to be used in the clinical trial should define their acceptance criteria together with the tests used to exert sufficient control of the quality of the active substance. Tests and defined acceptance criteria are mandatory for quantity, identity and purity and a limit of ‘record’ or ‘report results’ will not be acceptable for these quality attributes. A test for biological activity should be included unless otherwise justified. Upper limits, taking into account safety considerations, should be set for the impurities. Microbiological quality for the active substance should be specified.

As the acceptance criteria are normally based on a limited number of development batches and batches used in non-clinical and clinical studies, they are by their nature inherently preliminary and may need to be reviewed and adjusted during further development.

Product characteristics that are not completely defined at a certain stage of development (e.g. glycosylation, charge heterogeneity), or for which the available data is too limited to establish relevant acceptance criteria, should also be recorded. As a consequence, such product characteristics could be included in the specification, without pre-defined acceptance limits. The results should be reported in the Batch Analyses section (S.4.4).

Additional information for phase II and III clinical trials

As knowledge and experience increases, the addition or removal of parameters and modification of analytical methods may be necessary. Specifications and acceptance criteria

set for previous trials should be reviewed and, where appropriate, adjusted to the current stage of development.

S.4.2. Analytical procedures
The analytical methods used for all tests included in the active substance specification (e.g. chromatographic methods, biological assay, etc.) should be listed including those tests reported without acceptance limits. A brief description for all non-compendial analytical procedures, i.e. the way of performing the analysis, should be provided, highlighting controls used in the analysis.

For methods, which comply with a monograph of the European Pharmacopoeia (Ph. Eur.), , the pharmacopoeia of an EU Member State, the United States Pharmacopoeia (USP) or the Japanese Pharmacopoeia (JP), reference to the relevant monograph will be acceptable.

S.4.3. Validation of analytical procedure
Validation of analytical procedures during clinical development is seen as an evolving process.

Analytical procedures, which are either described in Ph. Eur., the pharmacopoeia of a Member State, USP or JP, or are linked to a product-specific monograph, are normally considered as validated.

For phase I and II clinical trials, the suitability of the analytical methods used should be confirmed. The acceptance limits (e.g. acceptance limits for the determination of the content of impurities, where relevant) and the parameters (specificity, linearity, range, accuracy, precision, quantification and detection limit, as appropriate) for performing validation of the analytical methods should be presented in a tabulated form. If validation studies have been undertaken for early phase trials, a tabulated summary of the results of analytical method validation studies could be provided for further assurance.

Information for phase III clinical trials
Validation of the analytical methods used for release and stability testing should be provided. A tabulated summary of the results of the validation carried out should be provided (e.g. results or values found for specificity, linearity, range, accuracy, precision, quantification and detection limit, as appropriate). It is not necessary to provide a full validation report.

S.4.4. Batch analyses
As specification may be initially be very wide, actual batch data are essential for quality assessment. For quantitative parameters, actual numerical values should be presented.

The focus of this section is to demonstrate the quality of the batches (conformance to established preliminary specification) to be used in the given clinical trial. For early-phase clinical trials, where only a limited number of batches of active substance have been manufactured, test results for relevant clinical and non-clinical batches should be provided, including those to be used in the clinical trial. For active substances with a longer production history, it could be acceptable to provide results for only a number of representative batches, if appropriately justified.

Batch number, batch size, manufacturing site, manufacturing date, control methods, acceptance criteria and the test results should be listed together with the use of the batches. The manufacturing process used for each batch and any differences in these processes should be identified.

A statement should be included whether the batch analyses data presented are from the batches that will be used in the clinical trial, or whether additional batches not yet manufactured at time of submission of the pharmaceutical data might be used.

S.4.5. Justification of specification

A justification for the quality attributes included in the specification and the acceptance criteria for purity, impurities, biological activity and any other quality attributes which may be relevant to the performance of the medicinal product should be provided. The justification should be based on relevant development data, the batches used in non-clinical and/or clinical studies and data from stability studies, taking into account the methods used for their control. It is acknowledged that during early clinical development, the acceptance criteria may be broader and may not reflect process capability. However, for those quality attributes that may impact patient safety, the limits should be carefully considered taking into account available knowledge (e.g. process capability, product type, dose, duration of dosing etc.). The relevance of the selected potency assay and its proposed acceptance limits should be justified.

Changes to a previously applied specification (e.g. addition or removal of parameters, widening of acceptance criteria) should be indicated and justified.

S.5. Reference standards or materials

Due to the nature of biologically / biotechnology-derived products a well-characterised reference material is essential to ensure consistency between different batches but also to ensure the comparability of the product to be marketed with that used in clinical studies and to provide a link between process development and commercial manufacturing. The characterisation of the reference material should be performed with reliable state-of-the-art analytical methods, which should be sufficiently described. Information regarding the manufacturing process used to establish the reference material should be provided.

If more than one reference standard has been used during the clinical development, a qualification history should be provided describing how the relationship between the different standards was maintained.

If available, an international standard should be used as primary reference material. Each in-house working standard should be qualified against this primary reference material. However, it should be noted that the use of an international or Ph. Eur. standard might be limited to certain defined test methods, e.g. biological activity. If an international or Ph. Eur. standard is not available, an in-house standard should be established during development as primary reference material. The stability of the reference material should be monitored. This can be handled within the quality system of the company

S.6. Container closure system

The immediate packaging material used for the active substance should be stated. Possible interactions between the active substance and the immediate packaging should be considered.

S.7. Stability

Stability summary and conclusions (protocol/material and method)

A stability protocol covering the proposed storage period of the active substance should be provided, including specification, analytical methods and test intervals. The testing interval should normally follow the guidance given in ICH Q5C.

The quality of the batches of the active substance placed into the stability program should be representative of the quality of the material to be used in the planned clinical trial.

The active substance entered into the stability program should be stored in container closure system of the same type and made from the same materials as that used to store active substance batches to be used in the clinical trial. Containers of reduced size are usually acceptable for the active substance stability testing.

Studies should evaluate the active substance stability under the proposed storage conditions.

Accelerated and stress condition studies are recommended as they may help understanding the degradation profile of the product and support an extension of the shelf-life.

The methods used for analysing the stability-indicating properties of the active substance should be discussed, or cross-reference to S.4.3 made, to provide assurance that changes in the purity / impurity profile and potency of the active substance would be detected. A potency assay should be included in the protocol, unless otherwise justified.

A re-test period (as defined in ICH Q1A guideline) is not applicable to biological / biotechnology derived active substances.

Stability data / results

Stability data should be presented for at least one batch made by a process representative of that used to manufacture material for use in the clinical trial. In addition, supportive stability data on relevant development batches or batches manufactured using previous manufacturing processes should be provided, if available. Such batch data may be used in the assignment of shelf life for the active substance provided an appropriate justification of the representative quality for the clinical trial material is given.

The relevant stability data available should be summarised in tabular format, specifying the batches tested, date of manufacture, process version, composition, storage conditions, time-points, test methods, acceptance criteria and results.

For quantitative parameters, actual numerical values should be presented. Any observed data trends should be discussed.

Progressive requirements will need to be applied to reflect the amount of available data and emerging knowledge about the stability of the active substance during the different phases of clinical development. By phase III the applicant should have a comprehensive understanding of the stability profile of the active substance.

Shelf-life determination

The claimed shelf-life of the active substance under the proposed storage conditions should be stated and accompanied by an evaluation of the available data. Any observed trends should be discussed.

The requested storage period should be based on long term, real-time and real temperature stability studies, as described in ICH Q5C. However, extension of the shelf-life beyond the period covered by real-time stability data may be acceptable, if supported by relevant data, including accelerated stability studies and/or relevant stability data generated with representative material.

The maximum shelf-life after the extension should not be more than double, or more than twelve months longer than the period covered by real-time stability data obtained with representative batch(es). However, extension of the shelf-life beyond the intended duration of the long term stability studies is not acceptable.

Where extensions of the shelf-life are planned, the applicant should commit to perform the proposed stability program according to the presented protocol, and, in the event of unexpected issues, to inform NPRA of the situation, and propose corrective actions.

Prior knowledge including platform technologies could be taken into consideration when designing a stability protocol. However, on its own this data is not considered sufficient to justify the shelf-life of the actual active substance.

P INVESTIGATIONAL PRODUCT UNDER TEST

P.1. Description and composition of the investigational product

The qualitative and quantitative composition of the IP should be stated. The information provided should include:

- a short statement or a tabulation of the dosage form
- composition, i.e. list of all components of the dosage form and their amount on a per-unit basis (including overages, if any), the function of the components, and a reference to their quality standards (e.g. compendial monographs or manufacturer's specifications)
- description of accompanying diluent(s)
- an outline of the type of container and closure used for the dosage form and for any accompanying reconstitution diluent, if applicable

P.2. Pharmaceutical development

For early development there may be only limited information to include in this section.

A short description of formulation development, including justification of any new pharmaceutical form or excipient, should be provided.

For products requiring additional preparation (e.g. reconstitution, dilution, mixing), compatibility with the used materials (e.g. solvents, diluents, matrix) should be demonstrated and the method of preparation should be summarised (reference may be made to a full description in the clinical protocol).

It should be documented that the combination of intended formulation and packaging material does not impair correct dosing, ensuring for example that the product is not adsorbed to the wall of the container or infusion system. This is particularly relevant for low dose and highly diluted presentations. Where applicable, the reliable administration of very small doses in first-in-human studies should be addressed as laid down in the EMA Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07).

Manufacturing process development

Changes in the manufacturing process including changes in formulation and dosage form compared to previous clinical trials should be described. An appropriate comparability exercise should support significant changes, e.g. formulation changes. In this regard, expectations are similar to those described in S.2.6. This data should be sufficiently detailed to allow a proper understanding of the changes and assessment of possible consequences to the safety of the patient.

Any changes in the formulation during the clinical phases should be documented and justified with respect to their impact on quality, safety, clinical properties, dosing and stability of the medicinal product.

P.3. Manufacture

P.3.1. Manufacturer(s)
The name(s), address(es) and responsibilities of all manufacturer(s) for each proposed production site involved in manufacture, testing and batch release should be provided. In case multiple manufacturers contribute to the manufacture of the IP, their respective responsibilities should be clearly stated.

P.3.2. Batch formula
The batch formula for the batch(es) to be used for the clinical trial should be presented. This should include a list of all components. The batch sizes or range of batch sizes should be given.

P.3.3. Description of the manufacturing process and process controls
A flow chart showing all steps of the manufacturing process, including relevant IPCs (process parameters and in-process-tests), should be provided accompanied by a brief process description. The IPCs may be recorded as action limits or reported as preliminary acceptance criteria and the focus should be on safety relevant attributes. For other IPCs, monitoring might be appropriate and acceptance criteria and action limits do not need to be reported. During development, as additional process knowledge is gained, further details of IPCs should be provided and acceptance criteria reviewed.

Most products containing recombinant proteins and monoclonal antibodies are manufactured by an aseptic process, which is considered to be non-standard. Non-standard manufacturing processes or new technologies and new packaging processes should be described in sufficient detail. (see the Guideline on process validation for finished products - information and data to be provided in regulatory submissions, EMA/CHMP/CVMP/QWP/BWP/70278/2012).

Reprocessing may be acceptable for particular manufacturing steps (e.g. re-filtration) only if the steps are adequately described and appropriately justified.

P.3.4. Control of critical steps and intermediates
Tests and acceptance criteria for the control of critical steps in the manufacturing process should be provided. It is acknowledged that due to limited data at an early stage of development (phase I/II), complete information may not be available.

If holding times are foreseen for process intermediates, duration and storage conditions should be provided and justified by data in terms of physicochemical, biological and microbiological properties.

For sterilisation by filtration the maximum acceptable bioburden prior to the filtration must be stated in the application. In most situations NMT 10 CFU/100 mL will be acceptable. Test volumes of less than 100 mL may be used if justified.

P.3.5. Process validation
The state of validation of aseptic processing and lyophilisation should be briefly described, if applicable. The validation of sterilising processes should be the same standard as for product authorised for marketing. The dossier should particularly include information directly regarding the product safety, i.e. on bioburden and media fill runs.

P.4. Control of excipients

P.4.1. Specifications
References to Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP may be made. For excipients not covered by any of the aforementioned standards, an in-house specification should be provided.

P.4.2. Analytical procedures
In cases where reference to a pharmacopoeial monograph listed under P.4.1 cannot be made, the analytical methods used should be indicated.

P.4.3. Validation of the analytical procedures
Not applicable.

P.4.4. Justification of specification
For non-compendial excipients as listed above in P.4.1, the in-house specification should be justified.

P.4.5. Excipients of human or animal origin
For excipients of human or animal origin, information should be provided regarding adventitious agents safety evaluation (e.g. sources, specifications, description of the testing performed) and viral safety data according to the Guideline on virus safety evaluation of biotechnological investigational medicinal products (EMEA/CHMP/BWP/398498/05) in Appendix D, A.2. Furthermore, compliance with the note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01) should be documented in section A.2.

If human albumin or any other plasma derived medicinal product is used as an excipient, information regarding adventitious agents safety evaluation should follow the relevant chapters of the Guideline on plasma-derived medicinal products (CPMP/BWP/706271/2010). If the plasma derived component has already been used in a product with a Marketing Authorisation then reference to this can be made.

P.4.6. Novel excipients
For excipient(s) used for the first time in a medicinal product or by a new route of administration, full details of manufacture, characterisation and controls, with cross-references to supporting safety data (non-clinical and/or clinical), should be provided according to the active substance format (details in A.3).

P.5. Control of the investigational product

P.5.1. Specifications
The same principles as described for setting the active substance specification should be applied for the medicinal product. In the specification, the tests used as well as their acceptance criteria should be defined for the batch(es) of the product to be used in the clinical trial to enable sufficient control of quality of the product. Tests for content, identity and purity are mandatory. Tests for sterility and endotoxins are mandatory for sterile products. A test for biological activity should be included unless otherwise justified. Upper limits, taking safety considerations into account, should be set for impurities. They may need to be reviewed and adjusted during further development.

Acceptance criteria for medicinal product quality attributes should take into account safety considerations and the stage of development. Since the acceptance criteria are normally based on a limited number of development batches and batches used in non-clinical and clinical studies, their nature is inherently preliminary. They may need to be reviewed and adjusted during further development.

The analytical methods and the limits for content and bioactivity should ensure a correct dosing.

For the impurities not covered by the active substance specification, upper limits should be set, taking into account safety considerations.

Additional information for Phase III clinical trials
As knowledge and experience increases the addition or removal of parameters and modification of analytical methods may be necessary. Specifications and acceptance criteria set for previous trials should be reviewed for phase III clinical trials and, where appropriate, adjusted to the current stage of development.

P.5.2. Analytical procedures
The analytical methods for all tests included in the specification should be described. For some proteins and complex or innovative pharmaceutical forms, a higher level of detail may be required.

For further requirements refer to S.4.2.

P.5.3. Validation of analytical procedures
For requirements refer to S.4.3.

P.5.4. Batch analysis
As specifications may initially be very wide, actual batch data are essential for quality assessment. For quantitative parameters, actual numerical values should be presented.

The focus of this section is to demonstrate the quality of the batches (conformance to established preliminary specification) to be used in the clinical trial. For early phase clinical trials where only a limited number of batches have been manufactured, test results from relevant clinical and non-clinical batches should be provided, including those to be used in the clinical trial. For products with a longer production history, it could be acceptable to provide results for only a number of representative batches, if appropriately justified.

Batch number, batch size, manufacturing site, manufacturing date, control methods, acceptance criteria and the test results should be listed together with the use of the batches. The manufacturing process used for each batch should be identified.

A statement should be included whether the batch analyses data presented are from the batches that will be used in the clinical trial, or whether additional batches not yet manufactured at the point of submission might be used.

P.5.5. Characterisation of impurities
Additional impurities and degradation products observed in the IP, but not covered by section S.3.2, should be identified and quantified as necessary.

P.5.6. Justification of specifications
A justification for the quality attributes included in the product specification should be provided mainly based on the active substance specification. Stability indicating quality attributes should be considered. The proposed acceptance criteria should be justified.

P.6. Reference standards or materials
The parameters for the characterisation of the reference standard should be submitted, where applicable.

Section S.5 may be referred to, where applicable.

P.7. Container closure system

The intended primary packaging to be used for the IP in the clinical trial should be described. Where appropriate, reference should be made to the relevant pharmacopoeial monograph. If the product is packed in a non-standard administration device, or if non-compendial materials are used, description and specifications should be provided.

For products intended for parenteral use where there is potential for interaction between product and container closure system, more details may be needed (e.g. extractable/leachable for phase III studies).

P.8. Stability

The same requirements as for the active substance are applied to the medicinal product, including the stability protocol, stability results, shelf-life determination, including extension of shelf-life beyond the period covered by real-time stability data, stability commitment and post-approval extension. Stability studies should provide sufficient assurance that the IP will be stable during its intended storage period. The presented data should justify the proposed shelf life of the product from its release to its administration to patients. The stability protocol for the IP should take into account the knowledge acquired on the stability profile of the active substance.

Bracketing and matrixing approaches may be acceptable, where justified.

In-use stability data should be presented for preparations intended for use after reconstitution, dilution, mixing or for multidose presentations. These studies are not required if the preparation is to be used immediately after opening or reconstitution.

Appendix E: Labelling Requirements

The following table lists the particulars that should be included on the labels for the following cases, unless its absence can be justified:

§ 1 describes the particulars that shall be listed on both the primary packaging and the secondary packaging (except for the cases described in § 2 and § 3).

§ 2 describes the particulars that shall be included on the label of the primary package (or any sealed dosing device that contains the primary packaging) when the product is to be provided to the trial subject or the person administering the medication within a primary package together with secondary packaging that is intended to remain together. The secondary packaging carries the particulars listed in § 1.

§ 3 describes the particulars that shall be included in the primary packaging if the primary packaging takes the form of blister packs or small units such as ampoules on which the particulars required in § 1 cannot be displayed. Secondary packaging should be provided bearing a label with those particulars.

No.	Particulars	**§ 1 GENERAL CASE** For both the primary and secondary packaging	**§ 2 PRIMARY PACKAGING** Where primary and secondary packaging remain together throughout	**§ 3 PRIMARY PACKAGING** Blisters or small packaging units
			SECONDARY PACKAGING carries the particulars listed in general case	
a.	Name, address and telephone number of the sponsor, CRO or investigator (the main contact for information on the product, clinical trial and emergency unblinding)	✓ [1]	✓ [2]	✓ [2]
b.	Name of product/ code	✓	✓	✓
c.	Strength of active substance(s)	✓	✓	✓
d.	Pharmaceutical dosage form and pack size	✓	✓	Optional [3]
e.	Route of administration	✓	Optional [4]	Optional [4]
f.	Batch and/or code number to identify the contents and packaging operation	✓	✓	✓
g.	Protocol number	✓	✓	✓
h.	Trial subject identification number/treatment number and where relevant, the visit number	✓	✓	✓
i.	Directions for use (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product)	✓	-	-
j.	"For clinical trial use only" or similar wording	✓	-	-
k.	Storage conditions	✓	-	-
l.	Period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity.	✓	-	-
m.	"Keep out of reach of children" except when the product is for use in trials where the product is not taken home by subjects.	✓	-	-
n.	Source of IP e.g. gelatin capsule (Porcine/ Bovine)	✓ [5]	-	-

[1]The address and telephone number of the primary contact for information on the product, clinical trial and emergency unblinding need not appear on the label where the subject has been given a leaflet or card which provides these details and has been instructed to keep this in their possession at all times.

[2]The address and telephone number of the main contact for information on the product, clinical trial and emergency unblinding need not be included.

[3]The pharmaceutical dosage form and quantity of dosage units may be omitted.

[4]Route of administration may be excluded for oral solid dosage forms.

[5]The source of IP need not appear on the label where this information is stated on the informed consent form.

Additional note:

1. Symbols or pictograms may be included to clarify certain information mentioned above. Additional information, warnings and/or handling instructions may be displayed.

2. If it becomes necessary to change the use-by date, an additional label should be affixed to the IP. This additional label should state the new use-by date and repeat the batch number. It may be superimposed on the old use-by date, but for quality control reasons, not on the original batch number. This operation should be performed at an appropriately authorised manufacturing site. However, when justified, it may be performed at the investigational site by or under the supervision of the clinical trial site pharmacist, or other health care professional following national regulations. Where this is not possible, it may be performed by the clinical trial monitor(s) who should be appropriately trained. The operation should be performed in accordance with GMP principles, specific and standard operating procedures and under contract, if applicable, and should be checked by a second person. This additional labelling should be documented appropriately in both the trial documentation and in the batch records.

3. Other than those particulars listed below, the particulars listed in the table above may be omitted from the label of a product and made available by other means, for example by use of a centralised electronic randomisation system, use of a centralised information system (e.g. QR code), provided that the safety of the subject and the reliability and robustness of data are not compromised. This shall be justified in the protocol.

   § 1: Particular b, c, d, e, f, h, k, and l;

   § 2: Particular b, c, d, e, f, and h;

   § 3: Particular b, c, e, f, and h.

Appendix F: Format for Interim Report and End of Study Summary Report

Date:
Deputy Director
Centre of Product and Cosmetic Evaluation
National Pharmaceutical Regulatory Agency (NPRA),
Ministry of Health Malaysia,
Lot 36, Jalan Profesor Diraja Ungku Aziz,
46200 Petaling Jaya, Selangor.
(Attention: Investigational Product Evaluation and Safety Section)

Dear Sir/ Madam,

INTERIM/ END OF STUDY SUMMARY REPORT (whichever applicable)
<Title of the trial>,<Protocol number>, <Date of approval>

The following is a summary of the aforementioned trial conducted in the following site(s):

	Name of trial site*
Site Initiation Visit:	<**insert date**>
First Patient First Visit:	<**insert date**>
Last Patient First Visit:	<**insert date**>
Last Patient Last Visit:	<**insert date**>
Number of patients screened:	<**insert number**>
Number of screened failure:	<**insert number**>
Number of patients enrolled:	<**insert number**>
Number of patients withdrawn or prematurely terminated:	<**insert number**>
Number of ongoing patients:	<**insert number**>
Number of patients completed study:	<**insert number**>
Number of SUSAR:	<**insert number**>
Last batch of drug supplies collected back from site:	<**insert date**>
Last batch of drug supplies sent back to <**originating site**> for destruction <**insert date**> (Note: if the drug is destructed locally, replace this with relevant information)	
Site Closure Visit:	<**insert date**>
Date of the end of trial:	<**insert date**>

Is it an early trial termination? Yes/ No

- If yes, provide justification for early trial termination:
- Number of patients still receiving treatment at time of early termination and their proposed management:

Thank you.

Best Regards,

<Insert Name and Designation>
Clinical Research Associate/CTIL Holder/Sponsor/PI

*If the trial is performed in more than one trial site, please repeat and complete for each trial site

Appendix G1: Format for Country Level Drug Accountability Report

Study Title		
Protocol No.		
Trial Site(s) [1]	Eg. Hospital Kuala Lumpur, PPUM, etc	
Product's Name [2]	Eg. Drug X 5mg Tablet/Placebo to Match Drug X 5mg Tablet	
CTIL/CTX No.	Eg. PBKD/LK-20230101, PBKD/LK-20230102	
Total Approved Quantity by NPRA (including approved additional quantity)	Date of approval	Cumulative quantity approved (country level)
	20.8.22	150 boxes
	15.1.23	175 boxes

No.	Date	Batch Number	Airway Bill Number/ Invoice Number	Trial Site	Total Quantity Approved	Total Quantity Received	Balance
1	20.8.22				150		150
2	15.12.22	X123	1569B4321	PPUM		20	130
3	15.1.23				25		155
4	20.4.23	X124	1569B8888	HKL		80	75

(Signature)
……
(Name of CTIL/CTX Holder)
Date:

Page number/Total Page Number

Note:

1. Please list all the approved sites for country level report.

2. CTIL holder is required to submit a Country Level Drug Accountability Report for each product/item as listed in the Lampiran A including additional quantity. For example, the total quantity to be imported may appear as illustrated below in the Lampiran A:

Bil.	Nama Produk	Jumlah Kuantiti untuk Diimport
1.	Drug X 5mg Tablet/Placebo to Match Drug X 5mg Tablet	150 boxes*
2.	Drug X 10mg Tablet/ Placebo to Match Drug X 10mg Tablet	150 boxes*
3.	Drug X 25mg Tablet/ Placebo to Match Drug X 25mg Tablet	150 boxes*

*Each box contains 30 tablets

In the above-mentioned example, the CTIL/CTX holder is required to submit the Country Level Drug Accountability Report for each item listed above.

Appendix G2: Format for Manufacturing Drug Accountability Report

Study Title			
Protocol No.			
Manufacturer name and address	Eg. Company ABC, Jalan Universiti, 46200 Petaling Jaya, Selangor.		
Product's Name	Eg. Sildenafil Tablets 100mg		
CTX No.	Eg. CTX-220101		
Total Approved Quantity by NPRA (including approved additional quantity)	Date of approval	Batch Size	No. of Batches
	31.03.2022	100,000 tabs	2

No.	Date	Batch Size	Batch Number	Total Quantity Manufactured
1	02.05.2022	100,000 tabs x 1	2022SBE0101	100,000 tabs
2	08.08.2022	100,000 tabs x 1	2022SBE0108	200,000 tabs

(Signature)
……
(Name of CTX Holder)
Date:

Page number/Total Page Number

Appendix H1: CIOMS Form

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITALS (First, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6 REACTION ONSET Day	Month	Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTOIN
										☐ PATIENT DIED ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (Include generic name)		20. DID REACION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRO-DUCTION? ☐ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (From/to)	19. THERAPY DURATION	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (Exclude those used to treat reaction)
23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergies, pregnancy with last month of period, etc)

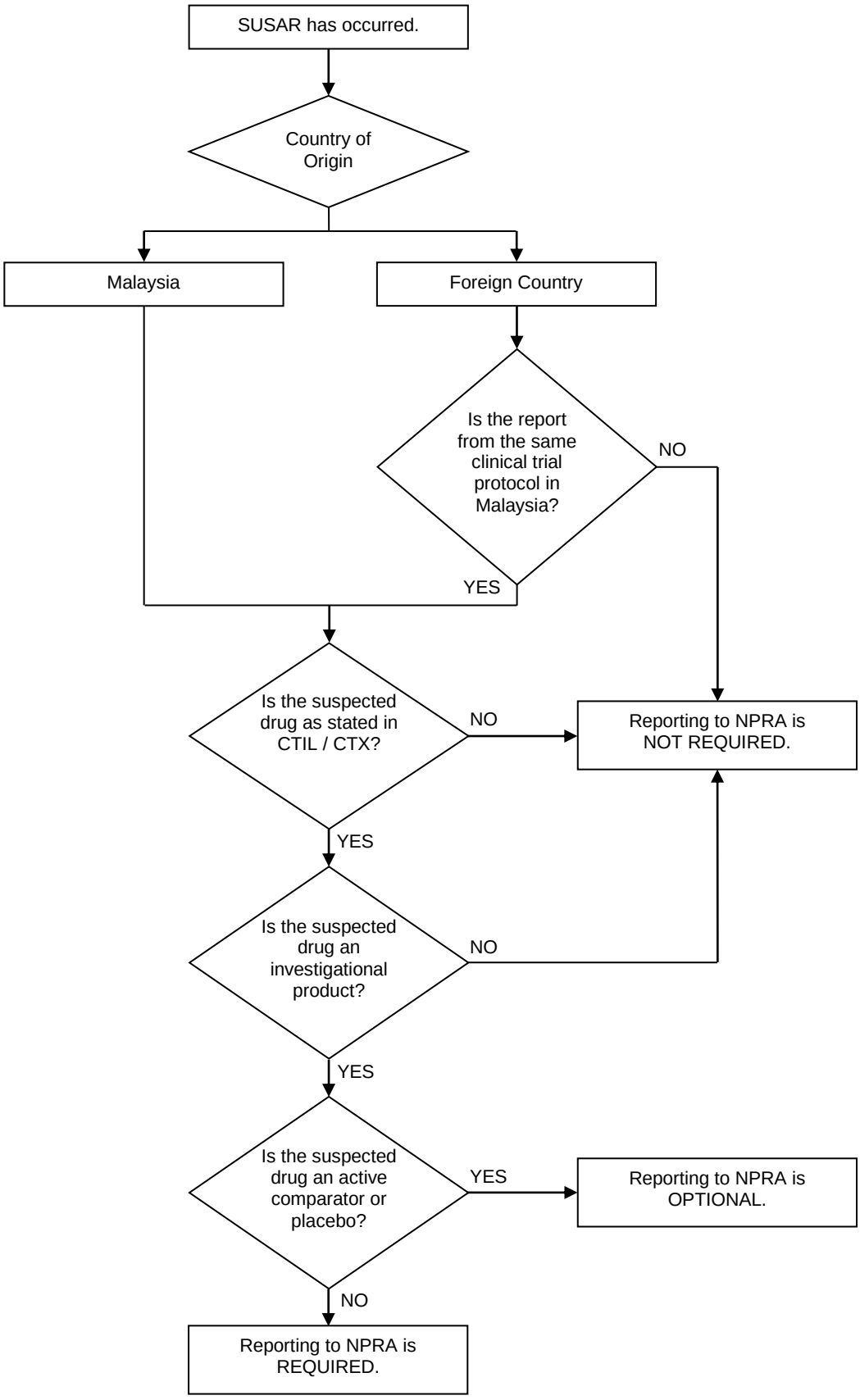
IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER	
	24b. MFR CONTROL NO.
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL
DATE OF THIS REPORT	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP

Appendix H2: Reporting Requirements and Timeline to NPRA

Nature of Report		Report? (Yes/No)	Timeframe of Report	Preferred Form	Content of Submission	Responsibility for Reporting
Clinical trial is not conducted in Malaysia.		No	Not Applicable			
Suspected drug is known to be active comparator, placebo or drug other than the investigational product.		No				
Serious Adverse Events (not drug related)		No				
Suspected Expected Serious Adverse Reaction		No				
For clinical trial conducted in Malaysia with CTIL/CTX	Suspected Unexpected Serious Adverse Reaction Death/Life Threatening Event	Yes	• Initial report as soon as possible but no later than 7 calendar days, followed by as complete a report as possible within additional 8 calendar days. • Follow-up information should be actively sought and submitted as it becomes available.	CIOMS-I	Where applicable: Cover letter Sponsor's comment	Sponsor
	Suspected Unexpected Serious Adverse Reaction Non-fatal/Non-Life Threatening Event	Yes	• Initial report as soon as possible but no later than 15 calendar days. • Follow-up information should be actively sought and submitted as it becomes available.	CIOMS-I	Where applicable: Cover letter Sponsor's comment	Sponsor

Appendix H3: Process of Qualifying SUSAR Reporting to NPRA



Appendix H4: Template of Cover Letter

Company Letterhead

Deputy Director
Centre of Product and Cosmetic Evaluation
National Pharmaceutical Regulatory Agency (NPRA)
Ministry of Health Malaysia
Lot 36, Jalan Profesor Diraja Ungku Aziz
46200 Petaling Jaya
Selangor
(Attention: Investigational Product Evaluation and Safety Section)

Dear Sir/ Madam,

SUBMISSION OF SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR) REPORT(S)

Study Drug:	
Study/Protocol ID/No.:	
Study Title:	

With reference to the above matter, we would like to submit the following SUSAR report(s) for review:

No.	CIOMS No.	SUSARs	Country of Origin	Report Type (Initial/Follow up)	Date of SUSAR	Date of Report
1						
2						
3						
4						
5						

Please find the enclosed copy of the SUSAR report(s).

Thank you.

Sincerely,

(Signature)
Full Name
Job Title/ Position
Company Stamp

Appendix I: World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor on-going studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

    and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive, as well as positive results, must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist, or other known interventions have been ineffective, the physician, after seeking expert advice,

with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

REFERENCES AND DIRECTIVES

References

1. European Commission (2010). Communication from the Commission - Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1) (2010/C 82/01).

2. European Commission (2011). The Rules Governing Medicinal Products in the European Union Volume 10 - Guidance Documents Applying to Clinical Trials Guidance on Investigational Medicinal Products (IMPs) and 'Non Investigational Medicinal Products' (NIMPs) (Rev. 1, March 2011)

3. EMA (2022). Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials. EMA/CHMP/BWP/534898/2008 Rev. 2.

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7. ICH (2005). Validation of Analytical Procedures: Text and Methodology Q2(R1). Current step 4 version, November 2005.

8. ICH (2016). Integrated Addendum to ICH (E6(R1): Guideline for Good Clinical Practice E6(R2). Current step 4 version, dated 9 November 2016.

9. MHRA (n.d). *MHRA Points to consider when preparing the IMP dossier*. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/317987/Points_to_consider_when_preparing_the_IMP_dossier.pdf

10. NCCR (2018). *Malaysian Guideline for Good Clinical Practice (4rd ed.).*

11. NPRA (2016). *Guidance Document and Guidelines for Registration of Cell and Gene Therapy Products (CGTPs) in Malaysia.*

12. PIC/S (2023). Annex 13 Manufacture of investigational medicinal products. *Guide to Good Manufacturing Practice for Medicinal Products Annexes (PE-009-17)*.

13. TGA (2021). Australian clinical trial handbook: Guidance on conducting clinical trials in Australia using ‘unapproved’ therapeutic goods. Version 2.4, August 2021.

14. WHO (2022). Guidelines on Evaluation of Biosimilars. Replacement of Annex 2 of WHO Technical Report Series, No. 977.

Directives

1. *KKM-55/203/001/D4 Bhg 4 (9)* dated 12 June 2007*. Keperluan Mendaftar Jawatankuasa Etika dengan Pihak Berkuasa Kawalan Dadah.*

2. *Direktif CT1-2009. KKM-55/201/005/01(15). Keperluan Mendaftar Penyelidikan Klinik dengan* National Medical Research Register (NMRR) *kepada* Sponsor/*Pemohon/Penyelidikan yang Memohon Lesen Import Percubaan Klinikal (CTIL) dan Kelulusan Mengilang (CTX).*

3. *KKM-55/BPF/401/007/02 (3)* dated 8 October 2010*. Keperluan Penyelidik Mengikuti Kursus/Latihan* Good Clinical Practice (GCP) *yang Diperakui oleh Jawatankuasa Penyelidikan Klinikal Kebangsaan (JPKK), Kementerian Kesihatan Malaysia (KKM).*

4. *Direktif Bilangan 1 Tahun 2011. (10) dlm. BPFK/PPP/01/03 Jilid 1. Direktif Penguatkuasaan Keperluan Kajian Bioekuivelens bagi Semua Produk Generik* Ïmmediate Release, Oral, Solid Dosage Form" *yang Mengandungi Bahan Aktif Racun Berjadual serta Akreditasi Pusat Kajian Bioekuivalens.*

5. *Surat Pekeliling Ketua Pengarah Kesihatan Malaysia Bil. 4/2015. KKM87/P1/26/10 jld.18 (41). Tatacara Prosedur Permohonan Berkaitan Penyelidikan Sel Stem dan Cell-Based Therapies.*

6. *Direktif Bilangan 9 Tahun 2016. BPFK/PPP/07/25 (40). 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.*

7. *Direktif Bilangan 11 Tahun 2016. (123) dlm. BPFK/30/05/1 Bahagian 4. Direktif Mengenai Penerimaan Pengesahan Pematuhan Amalan Perkilangan Baik (APB) bagi Tujuan Pendaftaran Semula Produk Farmaseutikal Berdaftar dengan Pihak Berkuasa Kawalan Dadah (PBKD).*

8. *Direktif Bilangan 4 Tahun 2019. (4) dlm. BPFK/PPP/07/25 Jld. 3. Direktif untuk Menerima Permohon Lesen Import Percubaan Klinikal (CTIL) dan Kebenaran untuk Mengilang Produk Tidak Berdaftar untuk Tujuan Percubaan Klinikal (CTX) yang Melibatkan Kajian* First-in-Human.

9. *Direktif Bilangan 12 Tahun 2020. NPRA.600-1/9/13 (3). Direktif Pelaksanaan Penilaian Keperluan Pemeriksaan Kajian Bioekuivalanes (BE).*

10. *Direktif Bilangan 22 Tahun 2021. NPRA.600-1/9/13 (32). Direktif untuk Menerima Permohonan Kebenaran Mengilang Produk Tidak Berdaftar untuk Tujuan Percubaan Klinikal (CTC) bagi Produk Vaksin Covid-19 Keluaran Pengilang Tempatan yang Menjalankan Penyelidikan dan Pembangunan (R&D) di Malaysia yang Melibatkan Kajian* First-in-Human (FIH).

11. *Direktif Bilangan 17 Tahun 2021. NPRA.600-1/9/13 (27). Direktif Berkenaan Keperluan Mendaftar Penyelidikan Klinikal Sukarelawan Sihat dengan* National Healthy Research Volunteer Register (NHRVR) *kepada* Sponsor/*Pemohon/Penyelidik yang Memohon Lesen Import Percubaan Klinikal (CTIL) dan Kelulusan Mengilang (CTX).*

12. *Direktif Bilangan 17 Tahun 2022. Direktif untuk Menerima Permohonan Lesen Import Percubaan Klinikal (CTIL) dan Kebenaran Mengilang Produk tidak Berdaftar untuk Tujuan Percubaan Klinikal (CTX) bagi Produk Biologik (Kecuali* Produk Cell and Gene Therapy) *yang Melibatkan Kajian Klinikal* First-in-Human (FIH).

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