7th Edition

2020

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

Bahagian Regulatori Farmasi Negara (NPRA)
Ministry of Health Malaysia

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

Bahagian Regulatori Farmasi Negara (NPRA)
Ministry of Health Malaysia
Lot 36, Jalan Universiti,
46200 Petaling Jaya,
Selangor Darul Ehsan.
Tel: 603-7883 5400

Second Edition	–	November 1993
Third Edition	–	December 2000
Fourth Edition	–	December 2004
Fifth Edition	–	June 2009
Sixth Edition	–	October 2014
Edition 6.1	–	September 2015
Edition 6.2	–	March 2016
Edition 6.3	–	July 2016
Edition 6.4	–	August 2017
Edition 7.0	–	August 2020

(Effective Date: 28 August 2020)

This Guideline is adapted from:

1. European Commission Detailed guidance for 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)
2. European Medicines Agency Guideline on the requirements for the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (EMA/CHMP/QWP/545525/2017)
3. Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials (EMA/CHMP/BWP/534898/2008 rev. 1 corrigendum)
4. ICH Q2 (R1) Validation of Analytical Procedures: Text and Methodology
5. MHRA Applying to conduct a clinical trial: Additional information
6. Pharmaceutical Inspection Co-operation Scheme Annex 13 Manufacture of investigational medicinal products PE 009-11 (Annexes)

THIS GUIDELINE IS ISSUED BY THE DIRECTOR OF PHARMACEUTICAL SERVICES UNDER REGULATION 29, CONTROL OF DRUGS AND COSMETICS REGULATIONS 1984. HE/SHE RESERVES THE RIGHT TO AMEND ANY PART OF THE GUIDELINE WHICHEVER HE/SHE DEEMS FIT.

FOREWORD

On par with the robust growth in clinical research landscape in Malaysia, the Bahagian Regulatori Farmasi Negara continues to take a proactive approach in optimising the regulatory process by streamlining the existing guideline with the current needs, regulatory requirements and international standards. Since the last publication of Guideline for the Application of Clinical Trial Import Licence (CTIL) and Clinical Trial Exemption (CTX) 6th Edition in 2014 to subsequent Edition 6.1, 6.2, 6.3 and 6.4 last published in 2017, there is a need for a revision to the guideline mentioned above to facilitate the industry better. Therefore, the current version intends to provide more comprehensive and up-to-date information that covers investigational product authorisation for clinical trial conducted in Malaysia.

The Malaysian Guideline for Application of CTIL and CTX 7th Edition supersedes the previous version of the guidance. This guideline shall also be read in conjunction with other guidelines relevant to the use of investigational products and clinical trial requirements. The current version of this guideline has incorporated (but not limited to) significant amendments regarding CTIL/CTX applications related to first-in-human trials. Adherence to this updated guideline will facilitate the CTIL, CTX and variation applications leading to timely approval by the Drug Control Authority.

I would like to extend my appreciation to the working committee and stakeholders for their contribution to the publication of the 7th Edition of the Malaysian Guideline for the Application of Clinical Trial Import Licence (CTIL) and Clinical Trial Exemption (CTX). With this latest guidance issued, we hope that it can better support the research and development of efficacious, quality and safe medicines for our population.

Dr Hasenah Binti Ali
Director
Bahagian Regulatori Farmasi Negara (NPRA)
Ministry of Health Malaysia

ACKNOWLEDGEMENTS

Advisor:
Dr Zaril Harza Zakaria
Head of Investigational Product Evaluation and Safety Section

Members of the Working Group:
Yam Pei Ching
Lee Wei Xin
Tan Shin Yee
Tang Sia Chin
Safiya Mohd Razif
Nur Atiqah Kamal Rodin
Nursafira Khiril Amir
Lin Hui Li
Aiza Adlina Abdullah
Wang Wai Meng
Cheong Ooi Jin

Bahagian Regulatori Farmasi Negara, Ministry of Health Malaysia would like to express gratitude to the stakeholders and individuals for their contribution and assistance in establishing and finalising this guideline.

TABLE OF CONTENTS

ABBREVIATION

ADR	Adverse Drug Reaction
AE	Adverse Event
ARC	Annual Retention Certificate
BE	Bioequivalence
CDCR	Control of Drugs and Cosmetics Regulations
CoA	Certificate of Analysis
CPCE	Centre of Product and Cosmetic Evaluation
CRO	Contract Research Organisation
CSR	Clinical Study Report
CTIL	Clinical Trial Import Licence
CTRI	Clinical Trials Registry- India
CTX	Clinical Trial Exemption
CV	Curriculum Vitae
DCA	Drug Control Authority
DPS	Director of Pharmaceutical Services
EC	Independent Ethics Committee/ Institutional Review Board
EMA	European Medicines Agency
EudraCT	European Clinical Trials Database
FIH	First-in-Human
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICTRP	International Clinical Trials Registry Platform
ICH	International Council on Harmonisation of Technical Requirements for Registration of 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
NMRR	National Medical Research Register
NPRA	Bahagian Regulatori Farmasi Negara
PD	Pharmacodynamics
PI	Principal Investigator
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PK	Pharmacokinetic
SUSAR	Suspected Unexpected Serious Adverse Drug Reaction
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.

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

Regarding a marketed medicinal products, ADR 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 a pharmaceutical 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 a medicinal (investigational) product, whether or not related to the medicinal (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.

Clinical Trial Exemption
An exemption issued under regulation 15 (5), Control of Drugs and Cosmetics Regulations 1984 by 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 Director of Pharmaceutical Services under regulation 12(1)(*c*) of the same Regulations which authorises the licensee to import any product for 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 object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

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 the sponsor to perform one or more of a sponsor's trial-related duties and functions.

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.

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.

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/ Natural Medicinal Products
Plant-derived materials or products with therapeutic or other human health benefits which contain either raw or processed ingredients from one or more plants/animals.

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 among 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 continuing review of trial protocol and amendments and of 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 including herbal/ natural/ animal medicinal products 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, or when used for an unapproved indication (off-label use), or when used to gain further information about an approved use.

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;
a. Alleviating, treating, curing or preventing a disease or a pathological condition or symptoms of a disease;
b. Diagnosing a disease or ascertaining the existence, degree or extent of a physiological or pathological condition;
c. Contraception;
d. Inducing anaesthesia;
e. Maintaining, modifying, preventing, restoring or interfering with, the normal operation of a physiological function;
f. Controlling body weight;
g. General maintenance or promotion of health or 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 for the purpose of coordinating and promoting 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.

Poison
Any substance specified by name in the first column 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 a preparation for 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 GCP 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.

Quantitation Limit
The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy. The quantitation limit is a parameter of quantitative assays for low levels of compounds in sample matrices, and is used particularly for the determination of impurities and/ or degradation products.

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
Product being approved by the Drug Control Authority.

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

Reproducibility
Reproducibility expresses the precision between laboratories (collaborative studies, usually applied to standardisation of methodology)

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
Specificity is 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 in Malaysia by the Drug Control Authority.

SECTION I

1. Introduction

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

This guideline is issued by DPS under regulation 29, 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 the regulation 7(1), CDCR 1984, except as otherwise provided in these Regulations, no person shall manufacture, sell, supply, import or 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 provide the following mechanisms that allow individuals to gain limited access to unregistered product 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 clinical trial involving products that require CTIL/CTX, the sponsor/ investigator shall not start the clinical trial until EC has issued a favourable opinion and approved by DCA.

First-in-Human (FIH) clinical trials refer to trial when a new active substance under development is administered to human for the first time. CTIL and CTX application for FIH clinical trials will be accepted by NPRA in stages. Currently, only investigational product (IP) involving a new chemical entity and/or herbal/ natural product with therapeutic claims will be accepted. Reference is made to the directive of DPS (4) dlm. BPFK/PPP/07/25 Jld.3. Clinical trials that involve testing for the following category of products will not be considered as FIH clinical trials:

i. Generic product.
ii. Registered traditional (herbal) product with an indication for "traditionally used" when being tested for therapeutic claims.

2. Registration of Clinical Trial with NMRR

All clinical trials that require CTIL/CTX must be registered with NMRR. Reference is made to Directive of DPS CT1-2009. Before submitting the CTIL/CTX application to NPRA, the applicant should obtain a unique full NMRR Registration Number from the NMRR website. Applicant who fails to register his/ her clinical trial with NMRR shall result in non-acceptance of the CTIL/CTX application.

Applicant is required to quote the NMRR Registration Number in all communication with NPRA.

3. Products that Require CTIL/CTX

Before commencing any clinical trial involving product(s) that requires CTIL/CTX and prior importation/ manufacturing product locally for the study, the investigator/ sponsor shall apply CTIL/CTX to NPRA. The following products will require a CTIL/CTX:

3.1 A product including placebo which is not registered with the DCA and are intended to be imported for clinical trial purpose.

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

3.3 A traditional product with a marketing authorisation with an indication for "traditionally used" when used for unapproved indication/ therapeutic claims for clinical trial purpose.

3.4 An unregistered product, including placebo manufactured locally for the purpose of the clinical trial.

4. Application Formalities for CTIL/ CTX

4.1 Who can apply for CTIL/CTX

4.1.1 An investigator

4.1.2 An authorised person from a locally registered pharmaceutical company/ sponsor/CRO with a permanent address in Malaysia.

Note:

- Application for CTIL/CTX containing a 'poison/ drug' should be made by a Poison Licence Type A holder for pharmacist in a private sector or ARC holder for public pharmacist.

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

4.2 Responsibility of the applicant

4.2.1 The applicant is responsible for the product and all information supplied in support of his/her CTIL/CTX application for his/her product. He/she shall be responsible for updating any information relevant to the product or application.

4.2.2 In a case where the applicant is not the manufacturer and where confidentiality prevents disclosure of certain information to the applicant, such information may be furnished to the DCA through the applicant in a sealed envelope marked 'CONFIDENTIAL'.

4.2.3 Any person who knowingly supplies any false or misleading information in connection with his/her application for CTIL/CTX commits an offence under regulation 13(4), CDCR 1984.

4.3 Submission of CTIL/CTX application

4.3.1 CTIL application

Applicant is advised to contact officers from Investigational Product Evaluation and Safety Section (IPESS), Centre of Product and Cosmetic Evaluation (CPCE) to schedule for an appointment to submit the CTIL application in person.

During the screening, IPESS officer will check for completeness of the CTIL application dossier and compliance with regulatory requirements. Submission checklist is available as a general guide. Incomplete application will be returned to the applicant.

Once the screening of the application dossier is found to be satisfactory, the applicant is required to proceed to Finance, Account & Revenue Section to make payment. The applicant is then required to provide the official receipt to IPESS in order for the application to be accepted.

4.3.2 CTX application

CTX application may be submitted by post or in-person to IPESS. Please refer to 4.3.1 for the procedure of applying in person.

For submission of application by post, complete CTX application should be forwarded to the following address:

Deputy Director
Centre of Product and Cosmetic Evaluation
Bahagian Regulatori Farmasi Negara (NPRA),
Ministry of Heath Malaysia,
Lot 36, Jalan Universiti,
46200 Petaling Jaya,
Selangor.
(Attention: Investigational Product Evaluation and Safety Section)

Application for CTX shall essentially be complete in the first instances based on the Submission Checklist. If the CTX application is deficient in any of the document, the applicant shall be informed in writing, and the CTX application dossier shall be returned as soon as possible.

4.4 Documents to be submitted in a new application for CTIL/CTX

4.4.1	**Table of content** A content page should be included in each CTIL/CTX application dossier. A template table of content can be found in Appendix A.
4.4.2	**Cover letter** The applicant shall submit a signed cover letter with the application. Its subject line should contain the full NMRR Registration Number and the protocol number 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** The applicant shall submit a complete application form with NMRR Registration Number. The application form shall be signed and dated by the applicant and stamped with the company's stamp. Application form for CTIL (current version PPPK/SPKPK/F01) and CTX (current version PPPK/SPKPK/F02) can be downloaded from NPRA website. Only one applicant and one local contact person from the same organisation, if any, can be named under Part 2 of the application form. All communication will be sent to the named applicant and the second contact person. For CTIL/CTX application involving FIH clinical trial, applicants are required to provide additional information as listed under Appendix D of the application form.
4.4.4	**Receipt for processing fee,** if applicable Every application for CTIL shall be accompanied by a processing fee. The CTIL application processing fee is RM 500.00 per product. CTIL application without the correct processing fee will not be processed. (See 4.3.1) The processing fee shall be paid in the form of bank draft/money order/postal order payable to 'Biro Pengawalan Farmaseutikal Kebangsaan'. Alternatively, the payment can be made using credit card at Finance, Account & Revenue Section. Note: Foreign currencies are not acceptable. The processing fee is not refundable. Application for CTX is free of charge.
4.4.5	A copy of **Company Registration Certificate,** if applicable The company must be registered with *Suruhanjaya Syarikat Malaysia*. The applicant (if said company is not the sponsor) should be authorised in writing by the sponsor to be the holder of the CTIL/CTX. Please refer to 4.4.7 for Letter of Authorisation. A copy of Company Registration Certificate is not required for investigator-initiated trial.
4.4.6	A copy of the applicant's **Poison Licence Type A** for pharmacist in the private sector or **ARC** for a public pharmacist, whichever applicable

4.4.7	**Letter of Authorisation**, if applicable
	
	• Letter of Authorisation should be submitted in cases where;
	  ○ Sponsor or a PI decides to use a service of 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/ hospital

	pharmacist. • A format of Letter of Authorisation in Appendix B may be used as a reference.
4.4.8	**A copy of the opinion(s) of the EC which is/are registered with DCA** • Applications for CTIL/CTX and EC can be submitted in parallel. The favourable opinion/ approval letter of EC (with attendance list) should be sent to the DCA as soon as possible when available. However, EC approval shall be provided at the point of submission for an expedited variation. • Following the directive issued by the DPS on *Keperluan Mendaftar Jawatankuasa Etika dengan Pihak Berkuasa Kawalan Dadah*, NPRA will only accept favourable opinion/ approval issued by EC that is registered with the DCA. Applicant is advised to refer the NPRA website for the current list of EC that is registered with DCA. For application involving FIH clinical trial, a positive opinion from EC shall be submitted to NPRA before the application can be tabled in the DCA meeting.
4.4.9	**Clinical trial protocol** The final version of a clinical trial protocol must be submitted. The version submitted should be the version which has been submitted to EC. The clinical trial protocol shall be in the format provided by Section 6, Malaysian Guideline for GCP and include the definition of the end of the trial. For 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, decision tree or diagram, which depicts the methodology must be stated in the study protocol.
4.4.10	**Declaration by investigator/ PI** Original copy of declaration by investigator/ PI of each trial site should be provided. Format for the document can be found in Appendix C. 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 investigator/ PI will be qualified by education, approved training in GCP and experience to assume responsibility for the proper conduct of the trial. The GCP certificate and CV for investigator/ PI of each trial site should be provided. • The GCP course should be recognised/ approved by NCCR, Ministry of Health Malaysia. The requirement is in accordance with the current version of Malaysian Guideline for GCP. • In case of BE study, GCP certificate and CV for clinical site investigator should also be provided if the investigator at the clinical site is not the PI.

4.4.12	**Informed consent form (Initial version only)** The ICF provided can be in either English or *Bahasa Melayu*. The initial version of ICF must be provided during submission.
4.4.13	**Pharmaceutical data for all 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: Investigational Products in Clinical Trials • Appendix D2: Modified Registered Comparator Products in Clinical Trials • Appendix D3: Investigational Products Containing Generics in Bioequivalence Studies • Appendix D4: Placebo Products in Clinical Trials • Appendix D5: Herbal/ Natural Products in Clinical Trials • Appendix D6: Biological Investigational Products in Clinical Trials **Shelf life and stability data** It is the responsibility of the applicant and sponsor to ensure that the product used is 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 comprise 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, i.e.: 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: • Specification against which the product is tested • Proposed extension based on available real-time data. Minimum 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/ ICH stability guidelines. For the First-in-Human Clinical Trial, a minimum of one (1) batch of stability studies under accelerated and real-time conditions for a minimum of 1 month should be provided. 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 (ICH Q1A (R2)).

	BE study For BE study, the test product should usually originate from a batch of at least 1/10 of production scale or 100,000 units, whichever higher, unless otherwise justified. **Appendix D3** *Section 4.S Drug Substance* shall be provided only for BE study involving chemical entity which has not been registered in Malaysia. **DCA-registered IP (Relabelling/ Secondary Packaging Modification)** In case IP used is a DCA-registered product, the applicant is not required to submit pharmaceutical data for the IP. However, a declaration letter from the sponsor to confirm that the quality of IP is the same as the DCA-registered product should be provided.
4.4.14	**Label for all products that require CTIL/ CTX** The applicant must ensure labels of products for clinical trial meet the labelling requirements, according to Appendix E. The particulars on the outer packaging of the investigational product, or where there is no outer packaging, on the immediate packaging, shall appear in *Bahasa Melayu* or English.
4.4.15	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 and repacker* should be submitted. The name and address of the manufacturer and/or repacker should be identical between the application form and GMP certificate provided. Any discrepancy in the information shall be justified. The certificate must be valid at the time of submission. For local manufacturer in Malaysia, a valid copy of *"Lesen Pengilang"* issued by NPRA should be submitted. <u>For Pharmaceutical Products:</u> For manufacturer in PIC/S member countries, a valid Certificate of GMP Compliance issued by participating authority of member countries shall be provided. For manufacturer from a non-PIC/S member country that has been inspected by a recognised regulatory authority, a valid Certificate of GMP Compliance issued by the inspecting regulatory authority shall be given. The recognised regulatory authorities are listed in Directive No. BPFK/PPP/07/25 (4) Jld. 1. For manufacturer in ASEAN countries, a valid Certificate of GMP Compliance issued by NDRA as mutually agreed in ASEAN Sectoral Mutual Recognition Arrangement (MRA) for GMP Inspection of Manufacturers of Medicinal Products shall be furnished. <u>For non-pharmaceutical products (e.g. herbal/ natural products and health supplements):</u> Certificate of GMP Compliance must be issued by an authority recognised by the DCA, i.e. the authorities listed in the World Health Organisation' Certificate Scheme on The Quality of Pharmaceutical Products Moving In International Commerce'. Note: For a manufacturer who 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 should

	be submitted to fulfil the requirement of GMP compliance. *Limited to 5 repackers for each product. **Note:** Other proof of GMP compliance documentation can be considered based on risk-based approach for the following conditions: 1) For manufacturer in PIC/S member countries for phase I clinical trial including FIH 2) For manufacturer in the US for all phases of clinical trial
4.4.16	**Investigator's Brochure** For content and format of the IB, reference is made to section 7, the current version of Malaysian Guideline for GCP. Unavailability of IB is generally acceptable for most of the BE study. However, IB shall 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	**Evidence of Phase 1 Unit Accreditation by NPRA** The Phase 1 Unit shall be on the NPRA Phase I Unit Accreditation Programme. Evidence of this listing shall be submitted for FIH clinical trial.
4.4.20	**Proof of Insurance Cover** Proof of insurance shall be submitted for FIH clinical trial for compensation of any damage suffered by subject resulting from participation in an FIH clinical trial.
4.4.21	**Declaration by Sponsor for CTIL/CTX Application Involving FIH Clinical Trial** Declaration by Sponsor shall be submitted in original copy for FIH clinical trial. A format for Declaration by Sponsor can be found in Appendix F.
4.4.22	**Electronic format** One electronic copy of application form, clinical trial protocol, pharmaceutical data and Investigator's brochure shall be submitted in a CD-ROM. Please refer to section 4.6.3 for preparation of the CD-ROM documents.
4.4.23	**Other or additional documents** Any other trial-related documents that could be relevant for the review of the clinical trial application by DCA may be submitted, e.g. published clinical data, if applicable.

4.5 Additional requirements

4.5.1 General requirements

Guidelines/ guidance issued by ICH, EMA and United States Food and Drug Administration may be served as a guide in the development process of a pharmaceutical.

The CTIL/CTX holder shall inform the DCA of any changes in information, or any information received by him/ her that casts doubt on the continued validity of the data which was submitted with or in connection with the application for the CTIL/ CTX.

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

4.5.2 Non-modified registered out of Malaysia comparator product

If the comparator product used is a non-modified, registered product in other country(ies) but not in Malaysia, approved package insert or document equivalent to the package insert, e.g. summary of product characteristics, can be submitted as supporting document in place of pharmaceutical data, certificate of GMP Compliance and investigator's brochure. Approved package insert provided should be from the country where the product is sourced from. Please ensure the manufacturer as stipulated in the package insert is the same as the manufacturer in the application form. Should the provided package insert does 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 comparator product

For comparator product that will be modified (e.g. repackaging, encapsulation), Appendix D2 and certificate of GMP Compliance (as in 4.4.15) for the manufacturer involved in the modification should be provided.

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.

Before initiating clinical development (e.g. Phase 1 trial), non-clinical studies should be available which 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 non-clinical studies should include (1) In vitro studies, many of which may already be available from quality-related bioassays, which are typically undertaken to establish comparability in reactivity and likely causative factor(s) if comparability cannot be verified and (2) In vivo studies which provide information on, including but not limited to, the PD effect and non-clinical toxicity (at least one repeat dose toxicity study). Toxicokinetics measurement should include determination of antibody titres, cross-reactivity and neutralising capacity. To support the CTIL/CTX application for a phase III clinical trials involving biosimilar product, the clinical comparability exercise data on clinical PK and PD study must be

available. In some instances, combined PK/ PD studies may be done in order to provide useful information on the relationship between exposure and effect.

4.5.5 **Cell and Gene Therapy Products (CGTPs)**

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

4.5.6 **Investigational product(s) containing psychotropic substance**

For application of CTIL intended for products containing psychotropic substance, the applicant is required to obtain Import Authorization from the Pharmaceutical Services Division after collection of CTIL.

4.5.7 **Manufacturing product(s) solely for clinical trial(s) in foreign country(ies)**

In addition to the documents as required in 4.4, the following documents should be supplemented for each participating foreign country(ies) when submitting a new CTX application.

4.5.7.1 Clinical trial registration number, e.g. ICTRP, EudraCT, CTRI, etc., if available.

4.5.7.2 Certificate of conformance/accreditation/approval letter of foreign BE centre, if the study concerned is a BE study.

Note: As the product(s) is/are manufactured solely for a clinical trial conducted outside 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. 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, please clearly label as number volume (e.g. 'volume 1/2', 'volume 2/2' etc).

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

4.6.2 Language

Application form must be filled 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* shall be submitted.

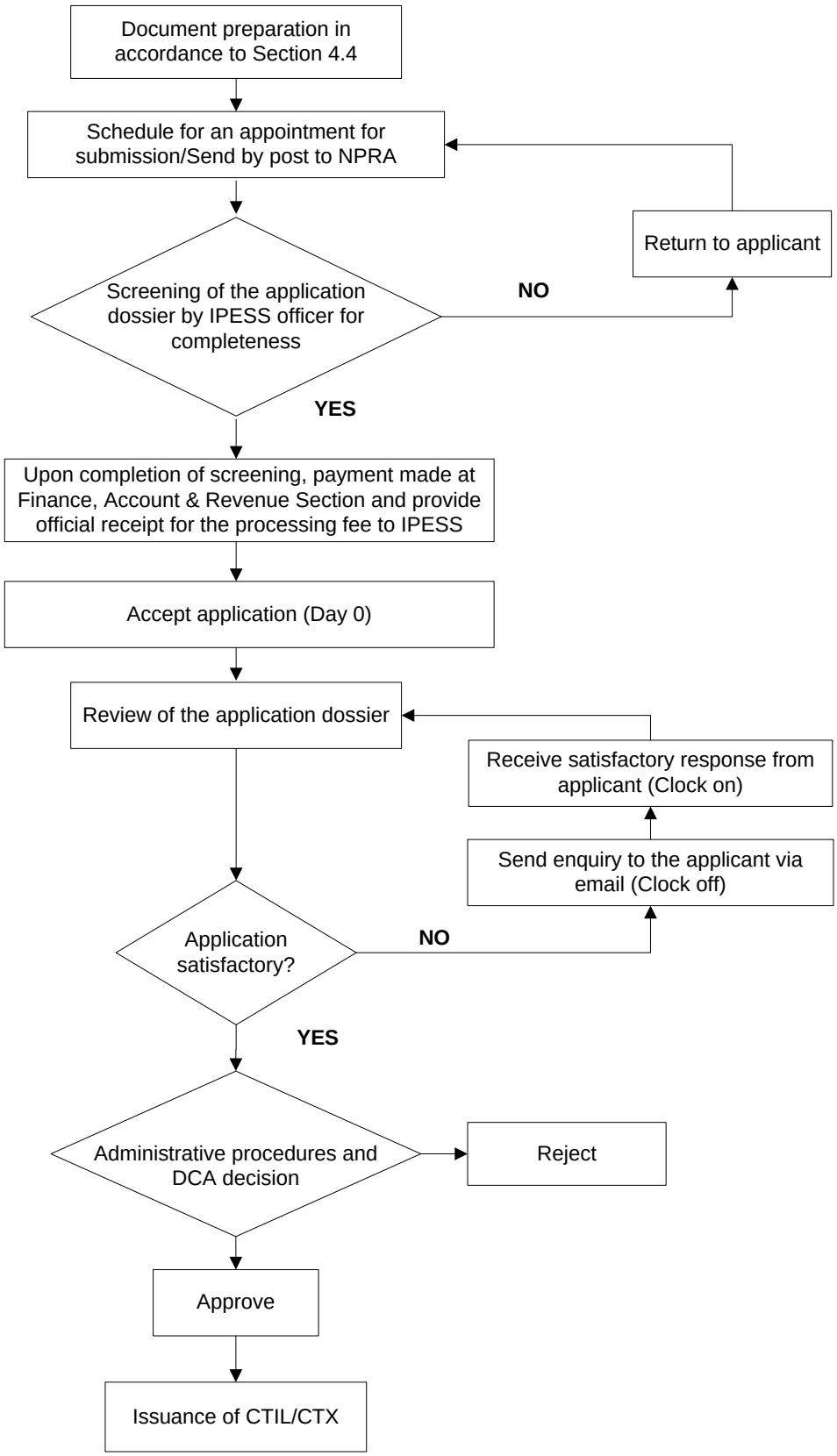
4.6.3 CD-ROM document submission

Electronic copy of documents shall be submitted in PDFs files with searchable text except for application form in Word version in a CD-ROM. The 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 done to create searchable text. In the event OCR routine is used, the applicant is responsible to ensure the quality of the text created is completely match to the original text. Applicant shall not submit password-protected documents or CD-ROM.

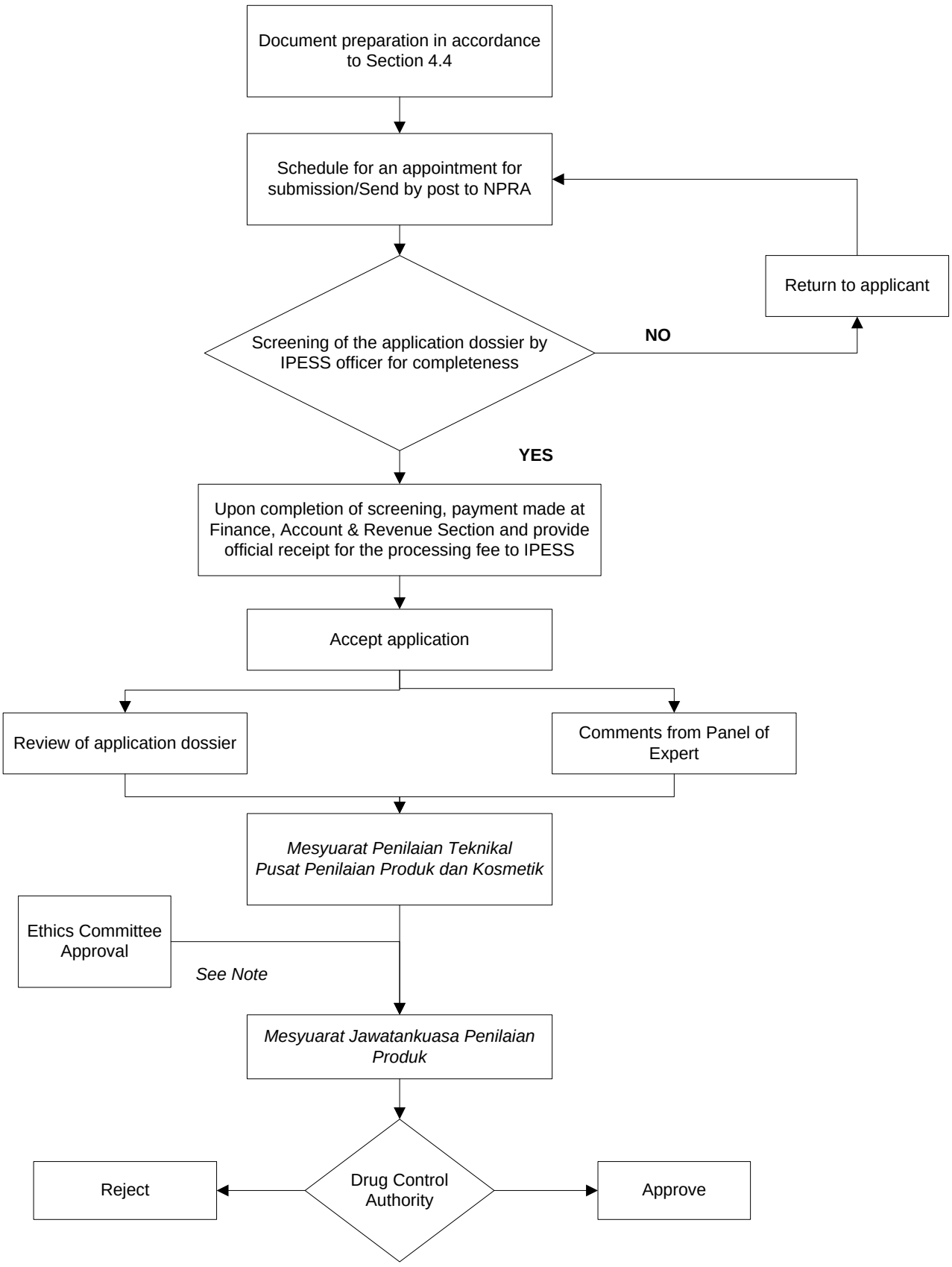
The envelope of the CD-ROM should be labelled clearly with document title, version number and date. Should more than one CD-ROMs be necessary, please clearly label as number volume (e.g. 'volume 1/2', 'volume 2/2' etc.).

5 Processing of CTIL/CTX Application

5.1 Flow Chart: CTIL/CTX application process



5.2 Flow Chart: CTIL/CTX application process involving First-in-Human Clinical Trial



Note:
Applications for CTIL/CTX and EC can be submitted in parallel. However, the application for CTIL/CTX involving FIH clinical trial will only be tabled to the DCA for deliberation once the favorable opinion from EC is received.

5.3 Timelines

Under normal circumstances, all CTIL/CTX application will be assessed within the following timeline:

- 45 working days for phase I trial, including FIH clinical trials, clinical trial involves biological/ biotechnological, cell therapy product and gene therapy product as well as herbal/natural product with therapeutic claim.

- 30 workings 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 query raised related to the application. The clock will stop on the day the query is e-mailed to the applicant. The applicant is expected to respond to the query within 30 working days. Should the answer received to the query is found to be unsatisfactory, only an additional 10 working days will be given for the applicant to provide a satisfactory answer. CTIL/CTX application will be rejected if NPRA does not receive adequate response/ reply for the queries or information requested by the evaluator after the 10 working days.

The timeline for FIH clinical trials of 45 working days only account for CTIL/CTX evaluation by NPRA; it does not include the review time taken by external Panel of Expert.

Fast-track reviews can be considered for application of new IP used for treatment/ prevention in pandemic/ epidemic situations in the interest of public health except for FIH clinical trials. Fast-track CTIL/CTX application will be assessed within the following timeline:

- 22 working days for phase I trial, clinical trial involves biological/ biotechnological, cell therapy product and gene therapy product as well as herbal/natural product with therapeutic claim.

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

5.4 Withdrawals of Application

Unexpected events or additional information may require the applicant to withdraw the CTIL/CTX application before the DCA has reached its decision on the application. The applicant should inform the NPRA as soon as he/ she becomes aware of the intention to withdraw the application. A formal letter of withdrawal providing a brief description of the reasons should be provided.

The processing fee is not refundable for withdrawn application.

6 Decisions of the DCA

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

The applicant shall come in person to collect the CTIL/CTX approval documents with the print out of CTIL/CTX 'ready for collection' e-mail. In the event that the applicant is unable to collect the document in person, the applicant shall provide a letter of authorisation with company letterhead for the authorised person to collect the approval documents on their behalf.

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

The 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 holder shall submit to the Drug Control Authority (DCA) a copy of Invoice / Delivery Order / Customs Declaration Form and evidence of delivery to the approved investigator(s) / trial centre(s) on importation and supply of each consignment of the product at the end of each study. Please refer to Appendix I for the format of Drug Accountability Report for Importation

The product shall only be supplied to the investigator(s) at the trial centre(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 centre shall be made without the prior approval of the DCA.

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

- The initial report should be submitted as soon as possible but no later than 7 calendar days for SUSARs which is fatal or life-threatening events and followed by an as complete a report as possible within 8 additional calendar days.

- For SUSARs, which is non-fatal or life-threatening events, the initial report should be reported as soon as possible but not later than 15 calendar days. Follow up information should be actively sought and submitted as it becomes available.

Note: Please refer to Malaysian Guideline for Safety Reporting of Investigational Products for specific requirement.

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

The CTIL/CTX holder shall inform the DCA of any change in information, or any information received by him/her that casts doubt on the continued validity of the data which was submitted with, or in connection with the application for the Clinical Trial Import Licence.

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

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

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

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

CTIL/CTX uncollected after 6 months of issuance shall be cancelled unless otherwise justified.

The CTIL/CTX holder is responsible for the safekeeping of the CTIL/CTX. In case of lost of CTIL/CTX, the holder is required to lodge in a police report immediately. The holder is required to write in to inform NPRA regarding the lost of CTIL/CTX accompanied with a certified true copy of the police report. Should CTIL/CTX is required for further importation/ manufacturing, a certified true copy of the CTIL/CTX will be provided to the holder, upon request.

8 Withdrawal of CTIL

In general, 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 shall state the reason(s) for the decision. The CTIL of the withdrawn product shall be invalid and returned. A new application (Refer to 4.3) shall be submitted if the IP is required again at a later date.

9 Reporting Amendment/ Update after CTIL/CTX Approval

9.1 Notification of amendment/ update

The holder of CTIL/CTX is responsible for notifying the DCA should there be any amendment/ update to the clinical trial protocol, pharmaceutical data, IB and other related documents. For the protocol amendment, the DCA must be notified after a favourable opinion from EC has been obtained for each site involved.

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

The DCA may request for further supplementary data or documentation when appropriate.

9.2 Notification administrative requirement

The notification of amendment/ update 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 shall be submitted in a CD-ROM format. The envelope of CD should be printed with protocol number and table of content (document title, version number and date).

   Please provide a separate cover letter for each clinical trial, where the amendment/ update affects more than one clinical trial of the same sponsor and the same IP.

9.3 Change of sponsor

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

a) a cover letter that includes the date of transfer of responsibilities
b) a letter on headed company paper from the current sponsor confirming the transfer of the study
c) a letter on 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

Any variation application can only be submitted once the application of CTIL/CTX has been approved. Valid CTIL/CTX is required for all variation application. Thus, the applicant is recommended to ensure the licence is valid throughout the whole study.

Please include the following documents in every application of variation:

a) Cover letter, including with a description of the variation application

b) Application form using current version attached with the relevant appendix

c) A copy of valid CTIL/CTX for all the products involved in the clinical trial

Each variation application (e.g. additional quantity, change of CTIL holder, etc.) must be submitted as a separate application. Therefore, please include the document as stated above (a-c), for each individual variation application. Every application should be bound in a management file/ binder, where appropriate.

10.1 Expedited variation

The expedited variation will be processed within 7 working days after receiving complete documents as listed in the table below:

No.	Variation Application	Documents Required
10.1.1	Change of investigator/ PI (See Note 1)	• Declaration by investigator/ PI (original copy) • GCP certificate for investigator/ PI • CV for investigator/ PI • EC approval/ favourable opinion (refer to 4.4.8)

10.2 Other variation

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

No.	Variation Application	Documents Required
10.2.1	Additional Quantity	• Justification of additional quantity • Calculation of quantity

		• Information of previously approved quantity for investigational product.
10.2.2	Additional Trial Site (See Note 1)	• Declaration by investigator/ PI of each trial site (original copy) • GCP certificate for investigator/ PI of each trial site. • CV for investigator/ PI of each trial site • EC approval/ favourable opinion (refer to 4.4.8) • Information of previously approved quantity for investigational product.
10.2.3	Change of CTIL holder (See Note 2)	• Change of CTIL holder within the **same company** a. Reason for the change of CTIL holder b. Poison Licence Type A / ARC • Change of CTIL holder to a **different company** a. Reason for the change of CTIL holder b. Poison Licence Type A / ARC c. Company registration certificate of the new licence holder d. Letter of Authorisation for Transfer of CTIL Holder. A format of this letter in Appendix G1 may be used as a reference. e. Statement of Acceptance. Format for Statement of Acceptance can be found in Appendix G2.
10.2.4	Additional Investigational Product, e.g. • Different Strength • Different dosage form • Different vial size • Different final volume	• Justification for additional investigational product • Calculation page • Pharmaceutical data (See Note 3) • CoA • Label • GMP Certificate (refer to 4.4.15) • Processing fee (refer to 4.4.4) • Official Receipt of Payment (See Note 4) • Information of previously approved quantity for investigational product.
10.2.5	Additional or Change Manufacturer/ Repacker	• GMP Certificate for the new manufacturer/ repacker (refer to 4.4.15)
10.2.6	New Protocol	• Letter of Authorisation, if applicable • Clinical trial protocol • Declaration by investigator/ PI of each trial site (original copy) • GCP certificate for investigator/ PI of each trial site. • CV for Investigator/ PI of each trial site • Calculation of quantity • ICF (initial version only) • Label • Overall risk and benefit assessment • EC approval/ favourable opinion (refer to 4.4.8)

10.2.7	CTIL Renewal (See Note 5)	• Processing fee (refer to 4.4.4) • Official Receipt of Payment (See Note 4) • Information of previously approved quantity for investigational product.
10.2.8	Change in Packaging	• Justification for the change in packaging • Calculation of quantity • Label • Stability Data (for change of primary packaging only)

Note 1: This application is not required for CTX application solely for a clinical trial conducted in a foreign country(ies).

Note 2: This application shall be submitted by the initial licence holder.

Note 3: For additional investigational product involving additional strength, dosage form, vial size and final volume, only pharmaceutical data for drug product is required. For additional investigational product due to other reasons, pharmaceutical data for both drug substance and drug product is required. If the additional IP is a comparator, please refer to 4.5.2 and 4.5.3.

Note 4: Applicant is required to proceed to Finance, Account & Revenue Section to make the payment for processing fee and a copy of official receipt has to be attached in the variation application.

Note 5: Application for CTIL renewal can be made within 6 months before the licence expiration date. All successful applications will be granted a renewal period of 3 years. However, the start date of the renewed licence will depend on the completed document submitted based on the following scenarios.

- Complete application accepted between 1 to 6 months BEFORE the expiration date, the start date of renewed licence will be continuous from the current licence.

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

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

- Application received accepted AFTER 3 months from the expiration date will not be processed. Applicant is advised to submit it as new CTIL application if necessary. (Refer to 4.3)

Variation application will be rejected if NPRA does not receive satisfactory response/ reply for the queries or information requested by the evaluator after 30 working days.

The applicant and second contact person, if available, shall be notified via e-mail the result of the variation application.

Approval letter uncollected after 6 months of issuance shall be cancelled unless otherwise justified.

11 Safety Decision Arising from Report Analysis / 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 action 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 be able to provide promptly clinical details of any individual overseas adverse drug reaction reports if requested by DCA.

12 Interim Report

In cases of trials lasting for more than six months, an interim report shall be submitted annually from the date of approval of CTIL/CTX until completion/ termination of the clinical trial. It is acceptable for a report to be submitted within the month that it is due. An interim report should be submitted for each trial site. Please refer to Appendix H for the format of an Interim Report.

13 Protocol Deviation

All significant 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 should be reported to DCA periodically.

Submission of protocol deviation(s) shall be standardised as follows:

- A cover letter in company letterhead is required for each submission.
- Protocol deviation report(s) attached to the e-mail shall be renamed according to the reference number and submitted in the format of an Excel file.
- Please refer to form GCLP/F-107 in NPRA's website for the format of submission.
- Hard copy or faxed documents relating to protocol deviation will not be accepted.

The CTIL/CTX holder shall be submit the protocol deviation(s) in soft copy via e-mail to:

mygcp@npra.gov.my

14 Trial Discontinuation

14.1 End of trial

The CTIL/CTX holder/ sponsor shall inform the DCA within 3 months from the last site closure in Malaysia. Subsequently, the CTIL/CTX holder/ sponsor shall also notify DCA when the full trial is completed, or the file/ data is frozen/ locked for international multicentre studies.

14.2 Early trial termination

The CTIL/CTX holder/ sponsor shall inform the DCA immediately or within 15 working days of early termination of the clinical trial in its entirety or at a clinical trial site. The reasons shall be clearly explained, and any follow-up measures taken for safety reasons shall be described.

The CTIL/CTX holder/ sponsor should return the CTIL/CTX as soon as possible.

14.3 Documents to be submitted at the end of the trial

14.3.1 End of Study Summary Report

The CTIL/CTX holder shall submit End of Study Summary Report pertaining to the site conducting the trial to the DCA within 3 months from the site closure. The report should be submitted for each trial site. Please refer to Appendix H for the format of the report.

14.3.2 Drug Accountability and Disposal Report

Drug Accountability and Disposal Report shall be submitted to DCA **within 3 months** from the site closure unless otherwise justified. The report should include

- Date(s) and quantity received for each product.
- Balance of the study medication(s)

Other documents to be included:

- Original CTIL/CTX, unless otherwise justified.
- *Borang A* for the relevant site (for CTIL application approved before 1st May 2012)
- Drug Accountability for Importation Report. Please refer to Appendix I for the format of the report.

Disposal / Return of Unused Investigational Product

- Confirmation on the local drug disposal or return of unused drug supplies to the country of origin or regional depot.
- For local disposal, all investigational products should be disposed of by the authorised bodies/ authority and documented. Destruction certificate should be provided as the evidence of destruction.

14.3.3 Clinical Study Report

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

The DCA shall be informed of any possible delay in 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-ROM format. The envelope of the CD should be printed with protocol number and table of content (document title, version number and date).

15 Archiving

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

16 Inspection by NPRA

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. The aims are to ensure the rights, safety and well-being of study subjects have been protected, to determine the validity of the data submitted to NPRA, to assure the integrity of scientific testing, and to ensure the legislation/ regulation, GCP principles and the Declaration of Helsinki (Appendix J) are complied with. Failure to allow NPRA to inspect may result in regulatory action such as product will not be registered or de-registered, and the investigator/ trial site will be blacklisted.

SECTION II: GUIDELINES ON APPENDIX

INTRODUCTION

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

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; neither 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.

6. These guidelines do not preclude any other information required by the DCA. Such additional information should be supplied to the DCA on request.

Appendix A: Format for Table of Content

Section	Description
1.	Cover letter
2.	CTIL/CTX application form
3.	3.1 Processing fee
	3.2 Company Registration Certificate
	3.3 Applicant's Poison Licence Type A for pharmacist in private sector or ARC for public pharmacist, whichever applicable
	3.4 Letter of Authorisation
4.	Opinion of the EC
5.	Clinical trial protocol
6.	Declaration by investigator/ PI (Original copy)
7.	GCP certificate and CV for investigator/ PI
8.	Informed consent form
9.	Pharmaceutical data for all products that require CTIL/ CTX
10.	Label(s)
11.	Certificate of GMP Compliance
12.	Investigator's brochure
13.	Overall risk and benefit assessment
14.	Scientific Advice from other regulatory agencies
15.	Phase 1 Unit Accreditation Certificate issued by NPRA (for FIH study only)
16.	Proof of Insurance Cover (for FIH study only)
17.	Declaration by Sponsor for CTIL/CTX Application Involving FIH Clinical Trial
18.	Electronic format (CD-ROM)
19.	Other or additional documents

Appendix B: Format for Letter of Authorisation

SPONSOR Letter Head (complete address, e-mail address 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 for:-

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

(Local applicant company's name) is authorised to be the Clinical Trial Import Licence Holder and will be responsible for all matters pertaining to the Clinical Trial Import Licence for the above-mentioned study protocol. In addition, the (Local applicant company's name) is authorised to conduct the following activities with regard to the above mentioned clinical trial:

	All tasks of the sponsor
	Monitoring
	Regulatory (e.g. preparation of applications to competent authority and ethics committee)
	Investigator recruitment
	IVRS– Treatment randomisation
	Data management
	E-data capture
	SUSAR reporting
	Quality assurance (QA) auditing
	Statistical analysis
	Medical writing
	Other duties subcontracted If yes to other please specify:

Thank you.

Sincerely,

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

Appendix C: Format for Declaration by Investigator/ Principal Investigator

Clinical Trial Title:

Protocol Number:

Name of Investigator/ Principal Investigator:

Name of the Trial Site:

A current Curriculum Vitae is attached.

1. I am aware of the responsibilities of my role as investigator/ principal investigator in the above-mentioned clinical trial as required by Malaysian Guideline for Good Clinical Practice, legal, ethical and 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 Bahagian Regulatori Farmasi Negara (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 guardian.

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 all requested trial-related records.

Investigator’s Signature:
NRIC No.: Date:
Official Stamp:

Appendix D: General Information for Pharmaceutical Data

1.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.

1.A.2 Adventitious Agents Safety Evaluation:

All materials of human or animal origin used in the manufacturing process of both drug substance and drug product, or such materials coming into contact with drug substance or drug product during the manufacturing process, should be identified. Information assessing the risk concerning 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.

TSE Certificates of suitability issued by the European Directorate for the Quality of Medicines & Health Care (EDQM) may be used as the basis of the risk assessments.

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.

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.

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

2.S DRUG SUBSTANCE

2.S.1 General Information:

2.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.

2.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.

2.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.

2.S.2 Manufacture:

2.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.

2.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 IMPD 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.

2.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.

2.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.

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

2.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).

2.S.3 Characterisation:

2.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.

2.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.

2.S.4 Control of the Drug Substance:

2.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.

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.

2.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, 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, 1.A.1General Considerations)

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

2.S.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.

2.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 all 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 2.S.2.2.

2.S.4.5 Justification of Specification(s)
For substances for which reference to a pharmacopoeial monograph listed under 2.S.4.1 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.

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

2.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.

2.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.

2.P INVESTIGATIONAL PRODUCT UNDER TEST

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

2.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 extemporaneously prepared medicinal products, e.g. products to be reconstituted or diluted before their use, the method of preparation should be summarised and reference made to a full description in the clinical protocol.

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.

2.P.3 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.

2.P.3 Manufacture:

2.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.

2.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.

2.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.

2.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 fewer 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.

2.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.

2.P.4 Control of Excipients:

2.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.

2.P.4.2 Analytical Procedures
Reference to pharmacopoeias should be indicated. In cases where reference to a pharmacopoeial monograph listed under 2.P.4.1 cannot be made, the non-compendial analytical methods used should be mentioned.

2.P.4.3 Validation of the Analytical Procedures
Not applicable.

2.P.4.4 Justification of Specifications
Not applicable.

2.P.4.5 Excipients of Animal or Human Origin
Refer to Appendix D, 1.A.2.

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.

2.P.5 Control of the Investigational Medicinal Product:

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

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.

For extemporaneously prepared medicinal products, 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.

2.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.

2.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.

2.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.

2.P.5.5 Characterisation of Impurities
Additional impurities/degradants observed in the IP, which was not covered by section 2.S.3.2, should be stated.

2.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.

2.P.6 Reference Standards or Materials:
The parameters for the characterisation of the reference standard should be submitted, where applicable.

Section 2.S.5 - Reference Standards or Materials - may be referred to, where applicable.

2.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.

2.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 DCA of the situation, including any corrective action proposed.

For preparations intended for multiple applications after reconstitution, dilution or mixing, in-use stability data should be presented. 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 First-in-Human Clinical Trial clinical trials

For **First-in-Human 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 IMP in the clinical study should be provided.

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

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.

3.P MODIFIED COMPARATOR PRODUCT

3.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.

3.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.

3.P.3 Manufacture:

3.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 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.

3.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.

3.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. 2.P.3.3.

3.P.4 Control of Excipients:

3.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.

3.P.4.2 Analytical Procedures
In cases where reference to a pharmacopoeial monograph listed under 3.P.4.1 cannot be made, the analytical methods used should be indicated.

3.P.4.3 Validation of Analytical Procedures
Not applicable.

3.P.4.4 Justification of Specifications
Not applicable.

3.P.4.5 Excipients of Animal or Human Origin
Refer to Appendix D, 1.A.2.

3.P.5 Control of the Modified Comparator Product:

3.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.

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

3.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.

3.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.

3.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").

3.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.

3.P.7 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.

3.P.8 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.

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

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

4.S DRUG SUBSTANCE

4.S.1 General information:

4.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.

4.S.1.2 Structure
The structural formula should be presented.

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

4.S.2 Manufacture:

4.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.

4.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.

4.S.3 Characterisation:

4.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.

4.S.4 Control of the Drug Substance:

4.S.4.1 Specifications

The 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 bioequivalence study.

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

4.S.4.2 Analytical Procedures
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, 1.A.1 General Considerations).

4.S.4.3 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. values found for repeatability, the limit of quantification, etc.). It is not necessary to provide a full validation report.

4.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.

4.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.

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

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

4.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.

4.P INVESTIGATIONAL PRODUCT UNDER TEST

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

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

4.P.3 Manufacture:

4.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 multiple manufacturers contribute to the manufacture of the IP, their respective responsibilities in the manufacturing chain should be clearly indicated.

4.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.

4.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.

4.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.

4.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.

4.P.4 Control of Excipients:

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

4.P.4.2 Analytical Procedures
Reference to pharmacopoeias should be indicated. In cases where reference to a pharmacopoeial monograph listed under 4.P.4.1 cannot be made, the non-compendial analytical methods used should be mentioned.

4.P.4.3 Validation of Analytical Procedures
Not applicable.

4.P.4.4 Justification of Specifications
Not applicable.

4.P.4.5 Excipients of Animal or Human Origin
Refer to Appendix D, 1.A.2.

4.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.

4.P.5 Control of the Investigational Medicinal Product:

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

4.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.

4.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.

Not applicable for CTX application.

4.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.

4.P.5.5 Characterisation of Impurities
Additional impurities/degradants observed in the IMP, but not covered by section 4.S.3.2, should be stated.

Not applicable for CTX application.

4.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.

Not applicable for CTX application.

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

Refer to Section 4.S.5 - Reference Standards or Materials, where applicable.

4.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.

4.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.

5.P PLACEBO PRODUCT IN CLINICAL TRIALS

5.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.

5.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.

5.P.3 Manufacture:

5.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.

5.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.

5.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.

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

5.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.

5.P.4 Control of Excipients:

5.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.

5.P.4.2 Analytical Procedures
Reference to pharmacopoeias should be indicated. In cases where reference to a pharmacopoeial monograph listed under 5.P.4.1 cannot be made, the non-compendial analytical methods used should be reported.

5.P.4.3 Validation of Analytical Procedures
Not applicable.

5.P.4.4 Justification of Specifications
Not applicable.

5.P.4.5 Excipients of Animal or Human Origin
Refer to Appendix D,1.A.2.

5.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.

5.P.5 Control of the Placebo Product:

5.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.

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

5.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.

5.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 / Natural Products in Clinical Trials

Note: This is the recommended format for clinical trials involving herbal/natural 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. Drug Substance (Standardisation Of Extract)

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 as such Phase 3 and Phase 4. For drug substance (standardisation of extract), details should be provided on the physical and phytochemical characterisation. Where applicable, details should be given on the biological activity.

2.3. Manufacturing of Drug Substance (Standardisation of Extract)

- 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)/ repacker(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

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

- 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

5.1 Specifications of the Drug Substance (Standardisation of Extract)
- Certificate of Analysis for drug substance (Standardisation Extracts) need to be attached (**minimum of 1 batch**).

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

5.2 Method of Identification of Marker Compounds in the Drug Substance (Standardised Extracts)

5.3 Method of Analysis of Marker Compounds in the Drug Substance (Standardised Extracts)
- o Both of the method used for identification and analysis need to be explained.

5.4 Specifications of the Finished Products
- o Certificate of Analysis must be certified by the Quality Assurance Manager. Certificate of Analysis for the recent batch should be submitted (**minimum of 1 batch**).
- o 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 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 is required.
- For early phase trials (e.g. Phase 1 & 2), a stability protocol can be provided at the point of CTIL/CTX submission.

6.4 Outline of on-going or proposed stability studies.

*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

- Please refer to Appendix E.

- 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 in-process testing, should be given. The results of in-process testing may be recorded as action limits or reported as preliminary acceptance criteria. During development, as process knowledge is gained, further detail of in-process testing and the criteria 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.

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 adventitious agents safety information for biologically-sourced materials should be provided in Appendix D,1.A.2.

Source, history and generation of the cell-substrate
A summarised 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 guideline 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. The generation and characterisation of the cell banks should be performed following principles of ICH guideline 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,1.A.2 if needed.

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, as appropriate.

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,1.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. Process modifications may require adaptation of in-process and release tests, and thus these tests and corresponding acceptance criteria should be reconsidered when changes are introduced.

Comparability exercise
Depending on the consequences of the change introduced and the stage of development, a comparability exercise may be necessary to ensure that the change would not have an adverse impact on clinical characteristics of the product. The primary 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, it is recommended to use the investigational product representative of the material used in non-clinical studies (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.

For the desired product, all relevant information available on the primary, secondary and higher-order structure including post-translational (e.g. glycoforms) and other modifications 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 a suitable, reliable and qualified method. Lack of such an assay should be justified. It is recognised that the extent of characterisation data will further increase in later phases.

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 the 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
During the clinical trial phases, where process validation data are incomplete, the quality attributes to control the active substance are essential 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 for quantity, identity and purity are mandatory. A test for the biological activity should be included unless otherwise justified. Upper limits, taking safety considerations into account, should be set for the impurities. Microbiological quality for the active substance should be specified.

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

Product characteristics that are not entirely defined at a particular stage of development, 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 the active substance should be listed for all tests included in the specification (e.g. chromatographic methods, biological assay, etc.) 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.

For methods, which comply with a pharmacopoeia, 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 the pharmacopoeia's general chapter or are linked to a product-specific monograph, are typically 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 extensive, 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, which are often characterised by a limited number of batches, results for relevant non-clinical and clinical batches should be provided, including the results of batches to be used in the given clinical trial. However, with 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 time of submission of the IMPD 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 of IP 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 interaction 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 typically follow 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 containers that use the same type and materials of container closure system that is used for the active substance used to manufacture the clinical trial batch. 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 in understanding the degradation profile of the product and support extension of shelf-life.

Stability-indicating methods should be included in this stability protocol 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.

The re-test period (as defined in ICH Q1A guideline) does not apply to biological / biotechnology-derived active substances.

Stability data/ results

Stability data should be presented for at least one batch representative of the manufacturing process of the clinical trial material. Stability data of relevant development batches or batches manufactured using previous manufacturing processes could be provided. Such batch data may be used in the assignment of shelf life for the active substance provided appropriate justification of 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. For 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 a long term, real-time and real temperature stability studies, as described in ICH Q5C. However, an extension of the shelf-life beyond the period covered by real-time stability data may be acceptable, if supported and justified by relevant data, including accelerated stability studies.

The maximum shelf-life after the extension should not exceed two-fold and should not be more than twelve months beyond the provided stability data obtained with representative batch(es). However, extension 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 performing the proposed stability program according to the presented protocol, and, in the event of unexpected issues, to inform DCA of the situation, including any corrective actions proposed.

Prior knowledge, including platform technologies, could be taken into consideration when designing a stability protocol. However, on its own, it 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 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 of the medicinal product (e.g. reconstitution, dilution, mixing), the 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.

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 concerning 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 the manufacture, testing and batch release should be provided. In case 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(es) to be used for the clinical trial should be presented. This should include a list of all components to be used. 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 of all successive steps, including in-process testing, should be given. The results of in-process testing may be recorded as action limits or reported as preliminary acceptance criteria. During development, as process knowledge is gained, further detail of in-process testing and the criteria should be provided and acceptance criteria reviewed.

Most of the 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, periods 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 the aseptic processing and lyophilisation should be briefly described, if applicable. Taking into account EudraLex Vol. 4, Annex 13, 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
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
In cases where reference to a pharmacopoeial monograph listed under P.4.1 cannot be made, the non-compendial 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, 1.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.

P.5. Control of the investigational medicinal 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 the quality of the product. Tests for contents, identity and purity are mandatory. Tests for sterility and endotoxin are mandatory for sterile products. A test for the biological activity should be included unless otherwise justified. Upper limits, taking safety considerations into account, should be set for the 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 typically 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 safety considerations into account.

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 should be described for all tests included in the specification. 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 be initially 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, which are often characterised by a limited number of batches, results for relevant non-clinical and clinical batches should be provided, including the results of batches to be used in the given clinical trial. However, with 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 time of submission of the IMPD 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.

Refer to Section S.5 - Reference Standards or Materials 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 the 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.

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

Bracketing and matrixing approaches may be acceptable, where justified.

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

Appendix E: Labelling Requirements

The following table listed 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 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 investigational medicinal product. 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.

Appendix F: Format for Declaration by Sponsor for CTIL / CTX Application Involving First-in-Human Clinical Trial

Clinical Trial Title:

Protocol Number:

Name of Sponsor:

Investigational Product(s) Name:

1. I am aware of the responsibilities of my role as a sponsor in the above mentioned clinical trial as required by 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) against all actions, claims or proceedings in respect to any loss, injury or death of any person whomsoever arising out of or in connection with the aforementioned clinical trial.

3. I shall evaluate the safety of the Investigational Product(s) (IPs) being tested or used in the aforementioned clinical trial on an on-going basis and be fully responsible towards the safety of every subjects that have been dosed with the IP(s) in the clinical trial.

4. I shall ensure that the aforementioned clinical trial will not be commenced before written approvals have been received from the DCA and Medical Research & Ethics Committee (MREC).

Sponsor's Signature: Date:

Name of Undersigned: Official Stamp:

Appendix G1: Format for Letter of Authorisation for Transfer of CTIL Holder

SPONSOR Letter Head (full address, e-mail address, telephone and fax number)

Deputy Director
Centre of Product and Cosmetic Evaluation
Bahagian Regulatori Farmasi Negara (NPRA),
Ministry of Health Malaysia,
Lot 36, Jalan Universiti,
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) HOLDER

The above subject matter is referred.

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

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

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

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

3. Therefore, we hereby terminate the existing CTIL holder *Company name with business registration number and full address of the existing CTIL 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 holder*
Company of existing CTIL holder
} *(A copy of LOA shall be sent to these companies by the Sponsor)*

Appendix G2: Statement of Acceptance

STATEMENT OF ACCEPTANCE AS
CLINICAL TRIAL IMPORT LICENCE HOLDER

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

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

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

2. I hereby agree that I have sole responsibility for all matters pertaining to the CTIL 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 new applicant

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

Date:

Deputy Director
Centre of Product and Cosmetic Evaluation
Bahagian Regulatori Farmasi Negara (NPRA),
Ministry of Health Malaysia,
Lot 36, Jalan Universiti,
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>, <Name of trial site>, <Name of PI>

The following is a summary of the aforementioned trial conducted in the aforementioned 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

Appendix I: Format for Drug Accountability for Importation Report

Study Title		
Protocol No.		
Trial Site(s) [1]		
Product's Name [2]		
Clinical Trial Import Licence No.	PBKD/LK-	
Total Approved Quantity by NPRA (including approved additional quantity)	Date of approval	Total quantity approved

Table for Importation:

No.	**Date of Importation**	**Batch Number**	**Airway Bill Number/ Invoice Number** [3]	**Total Quantity Imported**	**Balance**

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

Note:

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

2. CTIL holder is required to submit a Drug Accountability for Importation Report for each product/item as listed in the approval letter for CTIL or additional quantity approval letter. For example, the total quantity to be imported may appear as illustrated below in the approval letter:

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 holder is required to submit three (3) copies of the Drug Accountability for Importation Report for each item listed above.

3. Please attach a copy of the invoice for each shipment.

Appendix J: 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, reestablishing 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.