KINGDOM OF CAMBODIA
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Ministry of Health

Guidelines on Registration of Therapeutic Product in Cambodia

Department of Drugs and Food

Adapted from ASEAN Common Technical Dossier (ACTD)

For inquiries, contact:

Department of Drugs, Food
1st Floor, Land Lot 80, Samdach Penn Nuth Blv. (Street 289),
Tuol Kork District, Phnom Penh

Phone : (855) 23 880 247
E-mail : info.campors@moh.gov.kh
Website: ddf.moh.gov.kh

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Document History

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Contents

Chapter A INTRODUCTION

1. Background

The Ministry of Health aims at ensuring that all drugs manufactured, imported or exported, distributed or sold in Cambodia are of acceptable quality, safety and efficacy. The process of product registration ensures that a pharmaceutical product is evaluated for its safety, efficacy and quality, prior to being registered by the Directorate of Pharmacy and released into the market. Therefore, all pharmaceutical products manufactured, imported, exported, distributed or sold in Cambodia should be registered.

The registration of drugs and related products in Cambodia is governed by Roay Kram promulgating the law on amendment of law on the Management of Pharmaceuticals 2007 No. 1207/037. These guidelines are intended to assist applicants in the process of applying for registration of pharmaceutical products in Cambodia.

This set of guidelines replaces all previous guidelines on pharmaceutical product registration distributed until 01 August 2019.

1.1. General Information

All pharmaceutical products must be registered before marketed in Cambodia. Products must be registered individually, with any differences requiring a separate registration application. These differences include the generic, brand name, dosage form, strength, specificity, sensitivity, manufacturer, country of manufacture, change in production method or any other alteration to a registered product. Different pack size can be applied in one application, however, applicant needs to submit labels, stability studies and other requirements for each pack size and require registration fee for each pack size.

The Department of Drugs and Food will compile and post the updated list of registered and deregistered products on CamPORS.

1.2. Responsibility of Applicant

Applicants (as defined in the glossary page 184) should note that they are responsible for the therapeutic product's quality, efficacy and safety throughout its life cycle. What this means is that the applicant's responsibilities start with the registration of the medicinal product and end when the product license expires or is cancelled. Since the product's quality, efficacy and safety can change at any time during the course of its life cycle, it is the applicant's responsibility to inform the Department of Drugs and Food when these changes occur as per the current guidelines.

The applicant should ensure that all information contained in their application is truthful and is not Misleading.

1.3. Application Process

Beginning from 01 August 2019 applications for registration and marketing authorization are made online at the Cambodia Pharmaceutical Online Registration System (CamPORS). The previous semi at

As of this date the Department of Drugs and Food will only accept registration of therapeutic products online via CamPORS. An applicant starts the online registration by opening the Department of Drugs and Food online registration Website ddf.moh.gov.kh, login at the local company portal. Applicant need to follow the instruction manual posted on the website to adequately and efficiently carry out the process. The applicant needs to have a valid email address that will be used as an official credential to using the system in the future and where a system generated temporary password is sent during the initial application.

The applicant must be a locally incorporated company, corporate or legal entity, with permanent address and registered at the Ministry of Commerce, Cambodia with the scope of business in pharmaceutical product. See also responsibility of applicants 1.2 above.

Applicant opens the CamPORS portal and click to applicable portals

- select 'Register Product' then
- based on the desired application type select: 'New Registration', 'License Renewal', or 'Apply for Variation'

Applicant must fill in all required information in the fields and click 'Select File' to upload all required and optional documents. Upon completion of the application it is necessary to press the "Submit" button in order to receive invoice and proceed to the next steps. The system generates and sends an invoice to the email used as credential to the applicant; the invoice will also be available for download when applicant login the Website.

Similarly, the system will issue application reference number confirming receipt submissions, which will be used as part of the registration number and unique identifier throughout the life cycle of registration.

1.4. Submission of Samples

When the system requests to send samples be delivered physically or mailed at

Ministry of Health
Department of Drug and Food
Registration Bureau
1st Floor, Land Lot 80,
Samdach Penn (Street 289)
Khan Tuol Kork Phnom Penh,
Kingdom of Cambodia.

Phone : (855) 23 880 247
E-mail : info.campors@moh.gov.kh
Website: ddf.moh.gov.kh

1.5. Applicable Fees

A non-refundable fee will be required upon submission of application for registration for each product. Upon submission of the application the system generates an invoice based on the current inter-ministerial Prakas : 1356 សហវ ប្រក Dated 18 December 2016on applicable fees for registration of pharmaceutical products. The applicant must print the invoice from system

for payment at a bank specified in this section.

Payment is to be made in any of the following methods:

- at the counter of an ACLEDA Bank as per invoice
- using QR-code for online payment via ACLEDA mobile app

After paying the invoiced fee at an ACLEDA Bank or online using QR-code the applicant needs to upload copy of the receipt onto the CamPORS platform. Applicant can use a scanner, a digital camera, or take a screenshot using a mobile phone to upload the receipt. The document must be in color & perfectly legible. Any content alterations using image processing software is prohibited and will trigger the failure of the verification. An officer (cashier) at single window will do verification of payment comparing the uploaded receipt against the bank statement and confirm payment. Applications will not be processed until payment has been verified.

After approval of payment both the applicant and the Drug Registration Bureau will be notified of the approval of payment via system generated email and the evaluation of the submission commence as DAY 1. The system will also request applicant to send sample of product to be registered.

1.6. Confidentiality

The confidentiality of information submitted to the Department of Drugs and Food will be preserved and DDF will protect submitted information against disclosure and unfair commercial use.

However, DDF will decide on the lawful use of information including:

- Release of certain information to other National Medicines Regulatory Authorities and to WHO, especially information relating to safety;
- Access to earlier records, for example during the evaluation of applications.

There will be an opportunity for the supplier of the documents to appeal against a proposed decision to release such information.

1.7. Timeframes

Submissions will be processed in succession based on the time of payment approval as day-one – Start Clock. Under exceptional circumstances applications may be fast-tracked due to a public health need or some other reason as the MoH may identify. [PRAKAS ON FAST TRACK APPLICATION SOCHEM]

If information provided is insufficient, a letter of deficiency requesting for additional information will be sent by email to the applicant and Stop Clock. This will delay the process of registration, so it is advisable that all the necessary information and required documents are provided and dossiers are prepared following the presentation format indicated in 2.1 and 2.2 below.

The following timeline indicates the expected length of time between applying for registration

and receiving the outcome.

Table 1: Registration Timeline

The registration timeline depends on the type of application and the completeness of the application.

Application submission	Screening process	Evaluation process	Regulatory Decision
New Chemical Entity	2 days	4 Months	2 month (Decided by committee meeting every 2 Months)
Generic product	2 days	3 Months	2 Months (committee meeting)
Minor Variation	2 days	2 weeks	2 weeks
Major Variation	2 days	1 Months	2 weeks
Renewal	2 days	6 weeks	2 Months (committee meeting)

1.8. Communication of decision

Once the review cycle is completed, a final conclusion can either be approval or rejection of the application.

The final decision can be on hold when the DDF seeks further information from the applicant, the manufacturer or other bodies such as WHO or national regualtory authorities of other countries. Applicant will be notified by email of the status of application and the reason of being on hold.

The therapeutic product applications that have been recommended for rejection the Drug Registration Bureau will notify applicant via email. To reduce the possibility of bias in registration decisions, and to enhance transparency, the reasons for rejection and the method to dispute a decision will be included in the event of unsuccessful applications.

For the therapeutic product applications that have been recommended for registration the Drug Registration Bureau will notify applicant via system generated email and a certificate of registration (Marketing Authorization) of the product will be issued one month after approval.

1.9. Drug Registration Code:

Application serial number will be issued confirming receipt of submission. They will be assigned in order of receipt and processed in succession. Registration numbers will be assigned as follows which includes the application serial number:

Code for first registration is composed of: **CAMNXXXXIP-YY**

Code for renewal is composed of: **CAMR1/R2XXXXIP-YY**

- CAM refers to Cambodia
- N refers to New Number
- XXXX refers to serial number
- IP refers Import Pharmaceutical
- LP refers Local Pharmaceutical
- R1 refers to First Renewal
- R2 refers to Second Renewal
- - (Hyphen)
- YY refers to Year of Registration eg. 19 means 2019

For Example CAMN0814IP-19

1.10. Suspension and revocation of marketing authorization

Under the following circumstances, marketing authorization can be suspended or revoked

- Strong safety concerns
- Unethical/inappropriate promotion
- Noncompliance with conditions of registration
- Composition deviates from that approved
- Post marketing surveillance report
- Revocation of the product from original country or any other regulatory authority

In the event of suspension or revocation, DDF will provide reasons and opportunity for appeal.

1.11. Appeals and complaints

In the event that an applicant wishes to contest a decision, they can appeal to the Department of Drugs and Food, Cambodia. Contact can be by email or in writing Director of Department of Drug and Food, Ministry of Health.

2. Preparation and Presentation of Technical Dossier for Submission

Applicant should submit an application for marketing authorization electronically using the format in this Guidelines. Dossier submissions that do not comply with these standards in this guideline will not accepted. The Department of Drug and Food has launched the Cambodia Pharmaceutical Online Registration System (CamPORS). In CamPORS applications are submitted online by filling the appropriate fields and uploading documents. All dossiers should be prepared in accordance to the format specified in this guideline as follows.

An applicant can upload up to 50 MB documents. If the size of the documents exceeds 50 MB the applicant should provide a link to google drive or drop box or other storage systems along with password to access (if any). The uploaded dossier should only contain data relating to one type of submission.

The full implementation of CamPORS will be on 1st of April 2020. A parallel system will continue until 31 March 2020. **After 31 March 2020 Dossiers submitted in paper or any form of portable electronic storage such as CD, DVD, or USB drive will not be accepted.**

2.1. Preparation of Electronic Data to Upload onto CamPORS

Throughout the preparation of the dossier, the display of information should be unambiguous and transparent, in order to facilitate the review of the basic data and to help a reviewer become quickly oriented to the application contents.

- Text and tables should be prepared using margins that allow the document to be printed on either A4 paper or Letter size (8.5 x 11cm)
- The left-hand margin should be sufficiently large that information is not obscured by the method of binding.
- Font and size for text and tables, should be (Times New Roman, 12-point font), i.e. large enough to be easily legible, even after photocopying.
- Every page should be numbered, with the first page of each part designated as page 1.
- Common technical acronyms and abbreviations should be defined the first time they are used in each part.
- Applicant shall submit electronically an application for marketing authorization using the format in this Guidelines on Submission of Common Technical Dossier
- References should be cited in accordance with the 1979 Vancouver Declaration on Uniform requirements for Manuscripts Submitted to Biomedical Journals.

2.2. Preparation of PDF documents for electronic submission

2.2.1. Application Forms

Applications are made by filling the required fields in CamPORS. Therefore, no application forms are provided. All required field should be filled either by directly typing into the fields or copying and pasting the information from other files such as MS-Word. The system may also request to upload already prepared documents. The following guidelines need to be followed in the preparation of documents to be uploaded.

2.2.2. Preparation of files in CSV Format to upload onto CamPORS

In an event where a table of data is needed, the system will request to upload the table in a comma delimited form as CSV format (Comma-Separated Value). The CSV format is meant to facilitate application where the data are automatically inserted fields as if they were typed. When a CSV file is required the system will generate a template for the preparation of that specific CSV file. The template contains the header of the table followed by few empty rows. The content of the headers should not be altered or repositioned because they have to be exact match with the CamPORS fields. To prepare the file the template is copied and pasted on a new empty MS-Excel spreadsheet at cell A1 position and the required rows are populated with the data. As many rows as the available data are filled and are saved as comma delimited i.e. *.csv (Not as Excel files *.xls or *.xlsx). The CSV file is then uploaded.

2.2.3. Preparation of searchable PDF files with OCR compatibility

All files containing technical data such as the Common Technical Dossiers (CTD) to be submitted by uploading on to CamPORS must be in Adobe Acrobat PDF format. All data should originate from electronic files rather than from scanned data. In order to process PDF

documents efficiently DDF assessors need to be able to easily navigate and manipulate the document (e.g. copy and pasting sections of the document or splitting a large document into multiple smaller documents). To facilitate this process the following points should be noted when creating PDF documents.

- All PDF documents should be created directly from Word or undergo Adobe Acrobat optical character recognition (OCR) at the time of creation.
- The technical documents should not be scanned as images. However, if applicants have to provide scanned PDF documents, it should be optical character recognition (OCR) scanned and searchable
- PDF documents to be uploaded onto CamPORS should not be file protected. In an event where the size of the documents exceeds 50 MB the applicant should provide a link to google drive or drop box or other storage systems along with password to access (if any).
- Fonts that are not supported by Microsoft Word should not be used on PDF documents.
- All PDF documents should be appropriately bookmarked to ensure that assessors can navigate directly to the sections of interest.

2.2.4. Preparation of non-searchable Image or PDF files

All documents where information is not extracted, but uploaded for the purpose of provision of evidence, including but not limited to certificates, sample pictures, photographs, hand written or stamped documents scanned as images, images created by graphic design software etc. can be directly uploaded as *.jpg images or converted in a PDF image before uploading. However, technical documents should not be uploaded as non-searchable images, the have to undergo OCR compatibility.

2.3.Language

The application and supporting documents shall be legibly typed in English, French or Khmer. Any document which is in any language other than English, French or Khmer must be accompanied by a certified or notarized full translation in addition to the copy that is in the original language. The accuracy of the translation is the responsibility of the applicant or marketing authorization holder. Authentication of the translation has to be done at the nearest consulate of Cambodia in the country from where the document originates.

3. Submission of Common Technical Dossier (CTD)

3.1.Preparation for Submission

In the preparation for the registration of a therapeutic product it is important for an applicant determine following points:

- the type of therapeutic product see 3.2 below
- the type of application to be followed
- the corresponding route of evaluation in 3.4 below

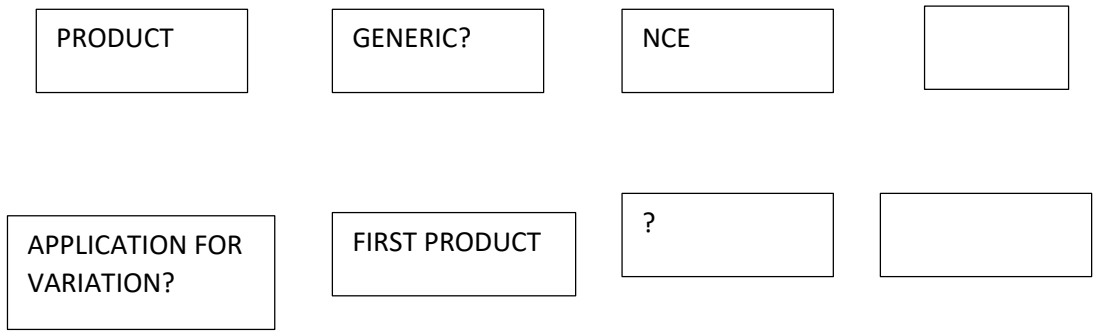

Figure 2 Schematic Diagram of Application Routes for Drug Registration

3.2.Product Types

A therapeutic product could contain either chemical or biological entity(ies) as the active ingredient(s).

A chemical entity refers to any chemical element, naturally occurring chemical material or chemical product obtained by chemical change or synthesis (including macromolecules produced by chemical synthesis, such as peptides/oligo-nucleotides), or any metabolites from a micro-organism (such as antibiotics).

[DEFINITION OF BIOTEC.]

A biological entity refers to any macromolecule extracted from an organism (such as proteins, nucleic acids, proteoglycans, cytokines and growth factors), or any substance derived from a biological system, including any of the following:

- a whole cell or micro-organism, such as a whole virus or bacterium used as a vaccine;
- a part of a micro-organism, such as a sub-unit vaccine;
- a plasma-derived product; or
- a biotechnology-derived substance, such as a protein or polypeptide.

3.3. Application Types

In applying for a therapeutic product, the type of application includes the following. Follow the instruction at the beginning of each chapter to proceed with the type of application.

- Dossier requirements for New Chemical Entity
- Dossier requirements for biotechnological products
- Dossier requirements for generic products

3.4. Dossier Evaluation Routes

Based on the type of application, the following three types of corresponding dossier evaluation route for registration of a product are to be pursued. Irrespective of intended route of evaluation the CamPORS platform is intended to facilitate data submission, and should be completed in all cases. Pharmaceutical products and related substances will be evaluated on at least three main accounts - safety, efficacy and quality. Evaluation process of some products may be fast-tracked due to a public health need or some other reason that DDF deemed necessary.

[FAST TRACK CIRCULAR SOHIEM OR THOL]

3.4.1. Full dossier evaluation

Full dossier evaluation applies to any product that has not been approved by any drug regulatory agency at the time of submission. After full dossier evaluation DDP shall prepare its own evaluation reports.

3.4.2. Abridged dossier evaluation

Abridged dossier evaluation applies to any product that has been evaluated and approved by *at least one* drug regulatory authority. Participating authorities of the Pharmaceutical Inspection Convention Pharmaceutical Inspection Co-operation Scheme (PIC/S) will be considered for abridged dossier evaluation. For abridged dossier evaluation DDF will rely on evaluation reports prepared by the national authorities which can be found at https://picscheme.org/en/members website.

Products not approved by the listed National Medicines Authorities will not be considered for abridged dossier evaluation unless exceptional circumstances exist that may make them appropriate for the Kingdom of Cambodia.

3.4.3. Verification dossier evaluation

Verification dossier evaluation applies to any product that has been evaluated and approved by the following Reference Medicines Regulatory Authorities. However, the DDF will have the final decision as to the appropriateness of the product for registration in Kingdom of Cambodia. DDF will rely on marketing authorization decisions made by the following reference Medicines

Regulatory Authorities for verification dossier evaluation in Cambodia:

Table 2: Reference Medicines Regulatory Authorities accepted for verification dossier evaluation[1]

Country/Region	Authority
Australia	Therapeutic Goods Administration (TGA)
Canada	Health Products and Food Branch Health (HPFB)
EU	European Medicines Agency (EMA)
Japan	Ministry of Health, Labour and Welfare of Japan
New Zealand	Medicines and Medical Devices Safety Authority (Medsafe)
USA	Food and Drugs Administration (FDA)
WHO	WHO Prequalified Products (POP)

3.5. Organization of Dossier

For any of the applications types indicated at 3.3 the Common Technical Document is organized into four parts as follows:

Part I. Administrative Data and Product Information

Part I contains initially the overall Table of Contents of the whole CTD to provide basically the information that could be looked through respectively. Secondly, the next content is the Administrative Data where required specific documentation in details is put together such as application forms, label, package insert etc. The last section of this part is Product Information where necessary information includes prescribed information, mode of action, side effects etc.

A general introduction to the pharmaceutical, including its pharmacologic class and mode of action should be included.

Part II. Quality Document

Part II should provide the Overall Summary followed by the Study Reports. The quality control document should be described in details as much as possible.

Part III. Nonclinical[2] Document

Part III should provide the Nonclinical Overview, followed by the Nonclinical Written Summaries and the Nonclinical Tabulated Summaries. The document of this part is not required for Generic Products, Minor Variation Products and some Major Variation Products. For ASEAN member countries, the Study Reports of this part may not be required for NCE Biotechnological Products and other Major Variation Products if the Original Products are

[1] Annex 11 Collaborative procedure in the assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities, https://www.who.int/medicines/areas/quality_safety/quality_assurance/TRS1010annex11.pdf

[2] The word “Nonclinical” replaces “Pre-clinical”

already registered and approved for market authorization in Reference Countries. However, the Department of Drugs and Food may request specific Study Reports when deemed necessary.

Part IV. Clinical Document

Part IV should provide the Clinical Overview and the Clinical Summary. The document of this part is not required for Generic Products, Minor Variation Products and some Major Variation Products. For ASEAN member countries, the Study Reports of this part may not be required for NCE, Biotechnological Products and other Major Variation Products if the Original Products are already registered and approved for market authorization in Reference Countries. However, the Department of Drugs and Food may request specific Study Reports when deemed necessary.

The overall organization of the Common Technical Dossier is presented on the following in Parts:

Part I: Administrative Information and Prescribing Information
- Section A: Introduction
- Section B: Overall Common Technical Dossier Table of Contents
- Section C: Documents required for registration (for example, application forms, labelling, Product Data Sheet, prescribing information)

Part II: Quality Document
- Section A: Table of Contents
- Section B: Quality Overall Summary
- Section C: Body of Data

Part III: Nonclinical Document
- Section A: Table of Contents
- Section B: Nonclinical Overview
- Section C: Nonclinical Written and Tabulated Summaries
  1. Table of Contents
  2. Pharmacology
  3. Pharmacokinetics
  4. Toxicology
- Section D: Nonclinical Study Reports
  1. Table of Contents
  2. Pharmacology
  3. Pharmacokinetics
  4. Toxicology

Part IV: Clinical Document
- Section A: Table of Contents
- Section B: Clinical Overview
- Section C: Clinical Summary
  1. Summary of Biopharmaceutics and Associated Analytical Methods
  2. Summary of Clinical Pharmacology Studies
  3. Summary of Clinical Efficacy
  4. Summary of Clinical Safety
  5. Synopses of Individual Studies
- Section D: Tabular Listing of All Clinical Studies
- Section E: Clinical Study Reports
- Section F: List of Key Literature References

Chapter B Part 1. CTD Administrative Data and Product Information

1. Scope of the Guideline

Part 1 of the dossier is intended to provide requirements for administrative data and product information for the registration of application for therapeutic product. Only Part 1 is general and appropriate for all the following types of applications:

- Dossier requirements for New Chemical Entity
- Dossier requirements for biotechnological products
- Dossier requirements for generic products

2. Required Data for Part 1 of CTD

Applicants should prepare Part 1 of the CTD using for any of the above types of application using the following format:

2.1. Introduction

A general introduction to the pharmaceutical, including its pharmacologic class and mode of action should be included.

2.2. Table of Content

Applicant should include a Table of Contents of the whole CTD to provide the information that could be looked through respectively.

2.3. Administrative Data and Product Information

This PART should be submitted by typing on the CamPORS portal or as an electronic copy (MS Word on a CD-ROM)?? and be properly cross-referenced to the dossier by clearly indicating to volume, page number in other parts and the title of all the supporting documents.

2.3.1. Applicant:

The application for the registration of a therapeutic product is made by the marketing authorization holder only.

Requirements in Company Registration: [to be inserts in appropriate section]

1. Letter of Authorization to register or import from the manufacturer to the application if appropriate

2. GMP Certificate from the country of origin

3. Certificate of pharmaceutical product from the country of origin (if available)

2.3.2. Manufacturer

The name, physical address, telephone number, fax number, and e-mail address of the applicant should be provided.

2.3.3. Generic name (INN)

Generic name should be included which is the internationally recognized non-proprietary name of such a therapeutic product.

2.3.4. Dosage form of the product

The dosage form of the product should be provided i.e. the form in which the therapeutic product is presented, e.g. solution, suspension, eye drops, emulsion, ointment, suppository, tablet, capsule, etc. For injections, the type of presentation e.g. vial, ampoule, dental cartridge, etc., and the type of content e.g. powder for reconstitution, solution, suspension, oily solution, etc.) should also be stated.

2.3.5. Brand Name and Label

Provide the brand name also referred to as trade name i.e. the name given by the manufacturer which is unique to a particular therapeutic product and by which it is generally identified and by which it is registered in the country of manufacture.

2.3.6. Strength of the product

Provide the strength of the product - given per unit dosage form or per specified quantity: e.g. mg/tablet (capsule), mg/mL, mg/5mL, mg/g etc.

2.3.7. Packing/Pack size of the product

Provide the Packing or Pack size of the product which is the presentation of the product to be registered i.e. list all pack sizes intended for marketing. Commercial pack size(s) for should be equivalent to a minimum full dose for the therapeutic indication.

2.3.8. Description of the therapeutic product

Visual Description of the therapeutic product should be included which includes a full visual description of the therapeutic product including colour, size, shape and other relevant features, marks, type of coating, scored, embossed etc.

2.3.9. Shelf life of the product

Provide the proposed shelf life of the product i.e. the specified length of time prior to use for which pharmaceutical products are inherently subject to deterioration are deemed to remain fit for use under prescribed conditions

2.3.10. Pharmacotherapeutic group and ATC code

Specify clinical indication(s) which are supported by relevant information in Parts 2, 3 and/or 4 of the application dossier. The Anatomical Therapeutic Chemical (ATC) Classification

System is used for the classification of therapeutic products. The classification system divides therapeutic products into different groups according to the organ or system on which they act and/or their therapeutic and chemical characteristics. Reference: https://www.whocc.no/atc_ddd_index/

The local applicant should be responsible for facilitating communication with the marketing authorization holder from the country of origin; and when the product is registered the local applicant should assume all legal responsibilities regarding the product on the Cambodian market.

2.3.11. Other Manufacturers

If there are multiple manufacturers, then the applicant should include names and addresses and their responsibilities relating to the therapeutic product (such as the manufacturing operation of each manufacturer in relation to the product being submitted).

2.3.12. Summary Product Characteristics (SmPC)

2.3.12.1. Product information for Health Professionals

Summary of Product Characteristics should be provided which is a summary of information about the product typically aimed towards medical practitioners and other health providers and which is approved by competent authority at the time of licensing.

EITHER refer TO WHO template or develop a new form not available in ASEAN

2.3.12.2. Patient information leaflet

Provide copies of all package inserts and any information intended for distribution with the product to the patient. The patient information leaflet (PIL) should be in conformity with the SmPC.

EITHER refer EMA template or develop a new form not available in ASEAN

Chapter C Part 2: CTD for New Chemical Entity (NCE)

Scope of the Guideline

Part 2 of the dossier is intended to provide guidance on the format of registration application for drug products regarding CTR. This chapter is appropriate for application of New Chemical EntityNCE.

Applicant should first complete dossier requirements Part 1 page 15 above which is general for any type of application.

Depending on the type of applicants for the remaining parts applicant should follow the following cross references

- Dossier requirements for New Chemical Entity go to page 19 Part 2: CTD for New Chemical Entity (NCE)
- Dossier requirements for biotechnological products go to page 31 Part 2: CTD for Biotechnological Product (Biotech)
- Dossier requirements for generic products go to page 43 Part 2: CTD for Generic Product (Generic)
- Dossier requirements for WHO Prequalified products go to page 53 Part 2: CTD for WHO Prequalified Product (WHO-PQP)
- Dossier requirements for products approved by Reference Regulatory Authority go to page 65 Part 2: CTD for Product Approved by Reference Regulatory Authority (RRA)

Part 2: Dossier Requirement (NCE)

Section A: Table of Content

A table of contents for the New Chemical Entity should be provided

Section B: Quality Overall Summary (QOS) (NCE)

The Quality Overall Summary (QOS) is a summary that follows the scope and the outline of the Body of Data in Section C below. The QOS should not include information, data or justification that was not already included in Section C below or in other parts of the common technical document (CTD).

Applicant should complete Quality Overall Summary (QOS) Chapter J page 175 relevant to type of application.

Section C: Body of Data (NCE)

S DRUG SUBSTANCE

S 1 General Information

S 1.1 Nomenclature

- International non–proprietary name (INN)
- Compendial name if relevant
- Registry number of chemical abstract service (CAS)
- Laboratory code (if applicable)
- Chemical name(s)

S 1.2 Structural formula

The structural, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided.

S 1.3 General Properties

A list should be provided of physicochemical and other relevant properties of the drug substance.

S 2 Manufacture

S 2.1 Manufacturer(s)

Name and full addresses including the city and country of the manufacturer of active ingredient.

S 2.2 Description of Manufacturing Process and Process Controls

The description of the medicinal substances manufacturing process represents the applicant's commitment for the manufacture of drug substances. The following information should be provided to adequately describe the manufacturing process and process controls:

A schematic flow diagram of the synthetic process(es) should be provided that includes molecular formulae, weights and yields, chemical structures of starting materials, intermediates, reagents and drug substance reflecting stereochemistry, and identifies operating conditions and solvents.

A sequential procedural narrative of the manufacturing process that provides quantities of raw materials, solvent, catalysts and reagent reflecting the representative batch scale, and includes process controls, equipment and operating conditions, such as temperature, pressure, pH, time etc.

Alternative process should be explained and described with the same level of details as the primary process. Reprocessing steps should be identified and justified.

S 2.3 Control of Materials

Material used in the manufacture of the drug substance (e.g., raw materials, starting materials,

solvents, reagents, catalysts) should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials (including biologically-sourced materials, e.g., media components, monoclonal antibodies, enzymes) meet standards appropriate for their intended use (including the clearance or control of adventitious agents) should be provided, as appropriate. For biologically-sourced materials, this can include information regarding the source, manufacture, and characterization.

S 2.4 Controls of Critical Steps and Intermediates

Critical steps: Tests and acceptance criteria, with justification including experimental data, performed at critical steps of the manufacturing process to ensure that the process is controlled.

Intermediates: Specifications and analytical procedure, if any, for intermediates isolated during the process.

S 2.5 Process Validation and/or Evaluation

Process validation or evaluation studies for aseptic processing and sterilization should be included.

S 2.6 Manufacturing Process Development

Description and discussion of significant changes made to the manufacturing process or manufacturing site of the drug substance used in producing non-clinical, clinical scale-up, pilot and if available, production scale batches should be included.

Reference ICH Guidelines: Q3A

[EMBAYE TO INCLUDE THE REFERENCE IN SECTIONS ABOVE IN THE FINAL EDIT]

S 3 Characterization

S 3.1 Elucidation of Structure and Characteristic

Confirmation of structure based on e.g. synthetic route and spectral analysis. Information on the potential for isomerism, the identification of stereochemistry, or the potential for forming polymorph should also be included.

Reference ICH Guidelines: Q6A

S 3.2 Impurities

Information on impurities should be provided.

Reference ICH guidelines: Q3A, Q3C, Q5C, Q6A and Q6B

S 4 Control of Drug Substance

Specification and justification of specification (s). Summary of analytical procedure and validation.

S 4.1 Specification

Detailed specification, tests and acceptance criteria for the drug substance should be provided.

Reference ICH Guidelines NCE: Q6A

S 4.2 Analytical Procedures

The analytical procedure used for testing the drug substance should be provided in sufficient detail to enable reproducible testing by another laboratory.

Reference ICH Guidelines: NCE: Q2A ; Biotech: Q6B

S 4.3 Validation of Analytical Procedures

Analytical validation information, including experimental data for the analytical procedure used for testing the drug substance should be provided. Typical validation characteristics to be considered are selectivity, precision (repeatability, intermediate precision and reproducibility), accuracy, linearity, range, limit of quantitation, limit of detection, robustness, and system suitability.

Reference ICH Guidelines: NCE: Q2A and Q2B ; Biotech: Q6B

S 4.4 Batch Analyses

Description of batches and results of batch analyses should be provided

Reference ICH Guidelines: NCE: Q3A, Q3C and Q6A ; Biotech: Q6B

S 4.5 Justification of Specification

Justification for the drug substance specification should be provided.

Reference ICH Guidelines: NCE: Q6A ; Biotech: Q6B

S 5 Reference Standards or Materials

Quality information of Reference standard or material used for testing of substance should be provided.

Reference ICH Guidelines: NCE: Q6A ; Biotech: Q6B

S 6 Container Closure System

A description of the container closure systems should be provided, including the identity of materials of construction of each primary packaging component, and each specification. The specifications should include description and identification (and critical dimensions with drawings where appropriate). Non-compendial methods (with validations) should be included where appropriate.

For non-functional secondary packaging components (e.g. those that do not provide additional protection nor serve to deliver the product), only a brief description should be provided. For

functional secondary packaging components, additional information should be provided.

The suitability should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the drug substance, including sorption to container and leaching, and/or safety of materials of construction.

S 7 Stability

Stability Summary and Conclusion

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate.

Reference ICH Guidelines: Q1A (R2), Q1B, and Q5C

Post-approval Stability Protocol and Stability Commitment

The post-approval stability protocol and stability commitment should be provided.

Reference ICH Guidelines: Q1A (R2) and Q5C

Stability Data

Results of the stability studies (e.g. forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphical, or narrative. Information on the analytical procedures used to generate the data and validation of these procedures should be included.

Reference ICH Guidelines: Q1A (R2), Q1B, Q2A, Q2B, and Q5C

P DRUG PRODUCT (NCE)

P 1 Description and Composition

A description of the drug product and its composition should be provided. The information provided should include, for example:

Description 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 reconstitution diluent(s); and

Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable.

Quantity should be stated in metric weight or measures.

Reference ICH Guidelines: NCE: Q6A ; Biotech: Q6B

P 2 Pharmaceutical Development

P 2.1 Information on Development Studies

The section of Pharmaceutical Development presents information and data on the development studies conducted to establish that the dosage form, the formulation manufacturing process, container closure system, microbiological attributes and usages instruction are appropriate for the purpose specified in the application. The studies described here are distinguished from routine control tests conducted according to specifications. Additionally, this section should identify and describe the formulation and process attributes (clinical parameters) that may influence batch reproducibility, product performance and drug product quality. Supportive data and result from specific studies or published literature may be included within or attached to the Pharmaceutical Development Section. Additional supportive data may be referenced to the relevant non-clinical sections of the application.

Reference ICH Guidelines: NCE: Q6A; Biotech: Q6B

P 2.2 Component of Drug Product

P 2.2.1 Active Ingredients

The compatibility of the drug substances with excipients listed in Item 2.1 should be discussed. Additionally, key physicochemical characteristics (e.g. Water content, solubility, particle size distribution, polymorphic or solid-state form) of the drug substance, which may influence the performance of the drug product should be discussed.

P 2.2.2 Excipients

The choice of excipients listed in Item P 1, their concentration and characteristics which influence the drug product performance, should be discussed relative to their respective function.

P 2.3 finished Product

P 2.3.1 formulation Development

A brief summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage. The differences between clinical formulations and the formulation (i.e. Composition) described in Item P 1 and P 2 should be discussed. Results from comparative in vitro studies (e.g. dissolution) or comparative in vivo studies (e.g., bioequivalence) should be discussed when appropriate.

P 2.3.2 Overages

Any overages in the formulation(s) described in Item P 1 should be justified.

P 2.3.3 Physicochemical and biological Properties

Parameters relevant to the performance of the drug product such as pH, ionic strength, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency and immunological activity should be addressed.

P 2.4 Manufacturing Process Development

The selection and optimization of the manufacturing process described in Item P 3.2, in particular its critical aspects, should be explained. Where relevant, the method of sterilization should be explained and justified.

Differences between the manufacturing process(es) used to produce pivotal clinical batches and the process described in Item P 3.2 that can influence the performance of the product should be discussed.

P 2.5 Container Closure System

The suitability of the container closure system used for the storage, transportation (shipping) and use of the drug product should be discussed as necessary. This discussion should consider e.g. choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form including sorption to container and leaching safety of materials of contraction, and performance such as reproducibility of the dose delivery from the device when present as part the drug product.

P 2.6 Microbiological Attributes

Where appropriate, the microbiological attributes of the dosage from should be discussed including the rationale for not performing microbial limits testing for non-sterile products, and the selection and effectiveness of preservatives systems in product containing antimicrobial preservatives. For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed.

P 2.7 Compatibility

The compatibility of the drug product or reconstitution diluents(s) or dosage devices, e.g. precipitation of drug substance in solution, sorption on injection vessels and stability should be addressed to provide appropriate and supportive information for the labeling.

P 3 Manufacture

P 3.1 Batch Formula

The formula with name and quantities of all ingredients (active and otherwise) including substance(s) which are removed in the course of manufacture should be included:

The actual quantities (g, kg, liters) etc. of ingredient should be stated.

Overage: Supporting data and the reason for including the overage shall be enclosed.

The total number of dosage unit per batch must be stated.

A description of all stages involved in the manufacture of the dosage form is required. Reference ICH Guidelines: Biotech: Q6B

P 3.2 Manufacturing Process and Process Control

A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified.

The full description of manufacturing process must sufficient details to cover the essential point of each stage of manufacture.

For sterile product the description includes preparation and sterilization of components. (i.e. Containers, closures, etc).

P 3.3 Controls of Critical Steps and Intermediates

Critical steps: Tests and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps identified P3.3 of the manufacturing process, to ensure that the process is controlled.

Intermediates: information on the quality and control of intermediates isolated during the process should be provided.

Reference ICH Guidelines: Q2A, Q2B, Q6A and Q6B

P 3.4 Process Validation and/or Evaluation

Description, documentation, and result of the validation studies should be provided from critical steps or critical assays used in the manufacturing process. (e.g. Validation of the sterilization process or aseptic processing or filling).

Reference: NCE: Q6B, Biotech: Q6B

P 4 Control of Excipients

P 4.1 Specification

The specification for the excipients should be provided.

Reference ICH Guidelines: NCE: Q6A; Biotech: Q6B

P 4.2 Analytical Procedures

The analytical procedures used for the testing the excipient should be provided, where appropriate.

Reference ICH Guidelines: NCE: Q2A; Biotech: Q6B

P 4.3. Excipients of Human and Animal Origin

For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g. sources, specifications, description of the testing performed, viral safety data).

(Reference ICH Guidelines: NCE: Q5A, Q5D ; Biotech: Q6B)

P 4.4 Novel Excipients

For excipient(s) used for the first time in a drug product or by a new route of administration, full details of manufacture, characterization and controls, with cross references to supporting safety data (nonclinical or clinical) should be provided

P 5 Control of finished Product

Specification and justification of the specification, summary of the analytical procedure and validation, and characterization of impurities.

P 5.1 Specification

The specification for the finished product should be provided.

Reference ICH Guidelines: NCE: Q6A; Biotech: Q6B

-P 5.2 Analytical Procedures.

The analytical procedures use for the testing the finished product should be provided.

Reference ICH Guidelines: NCE: Q2A ; Biotech: Q6B

P 5.3 Validation of Analytical Procedures

Description (including size, origin and use) and test result of all relevant batches e.g. pre-clinical, clinical pilot, scale-up, and if available production-scale batches) used to establish specification and evaluate consistency in manufacturing should be provided.

Reference ICH Guidelines: NCE: Q3A, Q3C, and Q6A; Biotech: Q6B.

Generics: refer to P.3.4.

P 5.4 Batch analyses

Description (including size, origin and use) and test result of all relevant batches e.g. pre-clinical, clinical pilot, scale-up, and if available production-scale batches) used to establish specification and evaluate consistency in manufacturing should be provided.

Reference ICH Guidelines: NCE: Q3A, Q3C, and Q6A; Biotech: Q6B.

Generics: refer to P.3.4.

P 5.5 Characterization of Impurities

P 5.6 Justification of Specification

Justification for the proposed finished product should be provided

Reference ICH Guidelines: NCE: Q3B and Q6A; Biotech: Q6B

P 6 Reference Standards or Materials

Requirement: Quality information and tabulated presentation of Reference standard or materials used for testing of drug product should be included.

Reference: NCE: Q6A, Biotech: Q6B

P 7 Container closure system

A description of the container closure systems should be provided, including the identity of materials of construction of each primary and secondary packaging component, and each specification. The specifications should include description and identification (and critical dimensions with drawings where appropriate). Non- compendial methods (with validations) should be included where appropriate.

For non-functional secondary packaging components (e.g. those that do not provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

Suitability information should be located in P 2.

P 8 Product Stability

Evidence is required to demonstrate that product is stable, meets the finished product specifications throughout its proposed shelf-life, that toxic decomposition products are not produced in significant amount during this period, and that potency, efficacy of preservative etc. are maintained.

Stability Summary and Conclusion

All criteria under ICH Guidelines are acceptable with the exception of real time storage conditions which should be 300C, 75% RH. Provision of moisture protection of the packaging should be taken into consideration.

Reference ICH Guidelines: Q1A (R2), Q1B, Q2A, Q2B and Q5C

Post-approval stability protocol and stability commitment

The post-approval stability protocol and stability commitment should be provided.

References ICH Guidelines: NCE, Biotech: Q1A (R2) and Q5C

Stability Data

Results of the stability studies should be presented in an appropriate format (e.g. tabular, graphical, narrative). Information on the analytical procedures used to generate the data and validation of these procedures should be included.
Reference: ASEAN Guideline on Stability Study of Drug Product, ASEAN Guideline on Validation of Analytical Procedure

P 9 Product Interchangeability

Not required for NCE

Section D: Key Literature References (NCE)

Key literature references should be provided, if applicable.

Chapter D Part 2: CTD for Biotechnological Product (Biotech)

Scope of the Guideline

Part 2 of the dossier is intended to provide guidance on the format of registration application for drug products regarding CTR. This chapter is appropriate for application of Biotechnological ProductBiotech.

Applicant should first complete dossier requirements Part 1 page 15 above which is general for any type of application.

Depending on the type of applicants for the remaining parts applicant should follow the following cross references

- Dossier requirements for New Chemical Entity go to page 19 Part 2: CTD for New Chemical Entity (NCE)
- Dossier requirements for biotechnological products go to page 31 Part 2: CTD for Biotechnological Product (Biotech)
- Dossier requirements for generic products go to page 43 Part 2: CTD for Generic Product (Generic)
- Dossier requirements for WHO Prequalified products go to page 53 Part 2: CTD for WHO Prequalified Product (WHO-PQP)
- Dossier requirements for products approved by Reference Regulatory Authority go to page 65 Part 2: CTD for Product Approved by Reference Regulatory Authority (RRA)

Part 2: Dossier Requirement (Biotech)

Section E: Table of Content

A table of contents for the Biotechnological Product should be provided

Section F: Quality Overall Summary (QOS) (Biotech)

The Quality Overall Summary (QOS) is a summary that follows the scope and the outline of the Body of Data in Section C below. The QOS should not include information, data or justification that was not already included in Section C below or in other parts of the common technical document (CTD).

Applicant should complete Quality Overall Summary (QOS) Chapter J page 175 relevant to type of application.

Section G: Body of Data (Biotech)

S DRUG SUBSTANCE

S 1 General Information

S 1.1 Nomenclature

- International non–proprietary name (INN)
- Compendial name if relevant
- Registry number of chemical abstract service (CAS)
- Laboratory code (if applicable)
- Chemical name(s)

S 1.2 Structural formula

The schematic amino acid sequence indicating glycosylation sites or other post-translational modifications and relative molecular mass should be provided, as appropriate.

S 1.3 General Properties

A list should be provided of physicochemical and other relevant properties of the drug substance, including biological activity for Biotech.

S 2 Manufacture

S 2.1 Manufacturer(s)

Name and full addresses including the city and country of the manufacturer of active ingredient.

S 2.2 Description of Manufacturing Process and Process Controls

The description of the medicinal substances manufacturing process represents the applicant's commitment for the manufacture of drug substances. The following information should be provided to adequately describe the manufacturing process and process controls:

Information on the manufacturing process, which typically starts with a vial(s) of the cell bank and includes cell culture, harvest(s), purification and modification reaction, filling storage and shipping conditions.

S 2.3 Control of Materials

Material used in the manufacture of the drug substance (e.g., raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials (including biologically-sourced materials, e.g., media components, monoclonal antibodies, enzymes) meet standards appropriate for their intended use (including the clearance or control of adventitious agents) should be provided, as appropriate. For biologically-sourced materials, this can include information regarding the source, manufacture, and characterization.

Control of source and starting materials of biological Origin.

Summaries of viral safety information for biologically -sourced materials should be provided.

Source, history and generation of the cell substrate.

Information of the source of the cell substrate and analysis of the expression construct used to genetically modify cells and incorporated in the initial cell clone used to develop the Master Cell Bank should be provided as described in Q5B and Q5D.

Cell banking system, characterization and testing.

Information on the cell banking system; quality control activities and cell line stability during production and storage (including procedures used to generate the Master and Working Cell Bank(s)) should be provided as described in Q5B and Q5D.

S 2.4 Controls of Critical Steps and Intermediates

Critical steps: Tests and acceptance criteria, with justification including experimental data, performed at critical steps of the manufacturing process to ensure that the process is controlled.

Intermediates: Specifications and analytical procedure, if any, for intermediates isolated during the process.

Additionally, for Biotech: Stability data supporting storage conditions should be submitted.

S 2.5 Process Validation and/or Evaluation

Process validation or evaluation studies for aseptic processing and sterilization should be included.

Sufficient information on validation and evaluation studies to demonstrate that the manufacturing process (including reprocessing steps) is suitable for its intended purpose and to substantiated selection of critical process controls (operational parameters and in- process test) and their limits for critical manufacturing steps (e.g. cell culture, harvesting, purification, and modification).

Information should include a description of the plan for conducting the study and the results, analysis and conclusions from the executed study(ies). The validation of corresponding assay and analytical methods should be cross-referenced or provided as part of justifying the selection of critical process controls and limits.

For manufacturing steps, intended to remove or inactive viral contaminants, the information from evaluation studies should be provided

S 2.6 Manufacturing Process Development

The developmental history of the manufacturing process, as described in S. 2.2, should be provided. The description of change(s) made to the manufacture of drug substance batches used in support of the marketing application (e.g. non-clinical or clinical studies) including for example, changes to the process or critical equipment. The reason for the change should be explained. Relevant information on drug substance batches manufactured during development, such as the batch number, manufacturing scale and use (e.g. stability, non clinical reference material) in relation to the change.

The significance of change should be assessed by evaluating its potential to impact the quality of the drug substance (and/or intermediate, if appropriate). For manufacturing changes that are considered significant, data from comparative analytical testing on relevant drug substance. A discussion of the data including a justification for selection of the test and assessment of results, should be included.

Testing used to assess the impact of manufacturing changes on the drug substance(s) and the corresponding drug product(s) may also include non-clinical and clinical studies in other modules of the submission should be included.

Reference ICH Guidelines: Q6B

S 3 Characterization

S 3.1 Elucidation of Structure and Characteristic

Details on primary, secondary and higher-order structure and information on biological activity, purity and immunochemical properties (when relevant).

Reference ICH Guidelines: Q6B

S 3.2 Impurities

Information on impurities should be provided.

Reference ICH guidelines: Q3A, Q3C, Q5C, Q6A and Q6B

S 4 Control of Drug Substance

Specification and justification of specification (s). Summary of analytical procedure and validation.

S 4.1 Specification

Detailed specification, tests and acceptance criteria for the drug substance should be provided.

Reference ICH Guidelines NCE: Q6A

Specify source, including as appropriate species of animal, type of microorganism, etc.

Reference ICH Guidelines: Q6B

S 4.2 Analytical Procedures

The analytical procedure used for testing the drug substance should be provided in sufficient detail to enable reproducible testing by another laboratory.

Reference ICH Guidelines: NCE: Q2A ; Biotech: Q6B

S 4.3 Validation of Analytical Procedures

Analytical validation information, including experimental data for the analytical procedure

used for testing the drug substance should be provided. Typical validation characteristics to be considered are selectivity, precision (repeatability, intermediate precision and reproducibility), accuracy, linearity, range, limit of quantitation, limit of detection, robustness, and system suitability.

Reference ICH Guidelines: NCE: Q2A and Q2B ; Biotech: Q6B

S 4.4 Batch Analyses

Description of batches and results of batch analyses should be provided

Reference ICH Guidelines: NCE: Q3A, Q3C and Q6A ; Biotech: Q6B

S 4.5 Justification of Specification

Justification for the drug substance specification should be provided.

Reference ICH Guidelines: NCE: Q6A ; Biotech: Q6B

S 5 Reference Standards or Materials

Quality information of Reference standard or material used for testing of substance should be provided.

Reference ICH Guidelines: NCE: Q6A ; Biotech: Q6B

S 6 Container Closure System

A description of the container closure systems should be provided, including the identity of materials of construction of each primary packaging component, and each specification. The specifications should include description and identification (and critical dimensions with drawings where appropriate). Non-compendial methods (with validations) should be included where appropriate.

For non-functional secondary packaging components (e.g. those that do not provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

The suitability should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the drug substance, including sorption to container and leaching, and/or safety of materials of construction.

S 7 Stability

Stability Summary and Conclusion

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate.

Reference ICH Guidelines: Q1A (R2), Q1B, and Q5C

Post-approval Stability Protocol and Stability Commitment

The post-approval stability protocol and stability commitment should be provided.

Reference ICH Guidelines: Q1A (R2) and Q5C

Stability Data

Results of the stability studies (e.g. forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphical, or narrative. Information on the analytical procedures used to generate the data and validation of these procedures should be included.

Reference ICH Guidelines: Q1A (R2), Q1B, Q2A, Q2B, and Q5C

P DRUG PRODUCT (Biotech)

P 1 Description and Composition

A description of the drug product and its composition should be provided. The information provided should include, for example:

Description 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 reconstitution diluent(s); and

Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable.

Quantity should be stated in metric weight or measures.

Reference ICH Guidelines: NCE: Q6A ; Biotech: Q6B

P 2 Pharmaceutical Development

P 2.1 Information on Development Studies

The section of Pharmaceutical Development presents information and data on the development studies conducted to establish that the dosage form, the formulation manufacturing process, container closure system, microbiological attributes and usages instruction are appropriate for the purpose specified in the application. The studies described here are distinguished from routine control tests conducted according to specifications. Additionally, this section should identify and describe the formulation and process attributes (clinical parameters) that may influence batch reproducibility, product performance and drug product quality. Supportive data and result from specific studies or published literature may be included within or attached to the Pharmaceutical Development Section. Additional supportive data may be referenced to the

relevant non-clinical sections of the application.

Reference ICH Guidelines: NCE: Q6A; Biotech: Q6B

P 2.2 Component of Drug Product

P 2.2.1 Active Ingredients

The compatibility of the drug substances with excipients listed in Item 2.1 should be discussed. Additionally, key physicochemical characteristics (e.g. Water content, solubility, particle size distribution, polymorphic or solid-state form) of the drug substance, which may influence the performance of the drug product should be discussed.

P 2.2.2 Excipients

The choice of excipients listed in Item P 1, their concentration and characteristics which influence the drug product performance, should be discussed relative to their respective function.

P 2.3 finished Product

P 2.3.1 formulation Development

A brief summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage. The differences between clinical formulations and the formulation (i.e. Composition) described in Item P 1 and P 2 should be discussed. Results from comparative in vitro studies (e.g. dissolution) or comparative in vivo studies (e.g., bioequivalence) should be discussed when appropriate.

P 2.3.2 Overages

Any overages in the formulation(s) described in Item P 1 should be justified.

P 2.3.3 Physicochemical and biological Properties

Parameters relevant to the performance of the drug product such as pH, ionic strength, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency and immunological activity should be addressed.

P 2.4 Manufacturing Process Development

The selection and optimization of the manufacturing process described in Item P 3.2, in particular its critical aspects, should be explained. Where relevant, the method of sterilization should be explained and justified.

Differences between the manufacturing process(es) used to produce pivotal clinical batches and the process described in Item P 3.2 that can influence the performance of the product should be discussed.

Generics: refer to P.3.2.

P 2.5 Container Closure System

The suitability of the container closure system used for the storage, transportation (shipping) and use of the drug product should be discussed as necessary. This discussion should consider e.g. choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form including sorption to container and leaching safety of materials of contraction, and performance such as reproducibility of the dose delivery from the device when present as part the drug product.

P 2.6 Microbiological Attributes

Where appropriate, the microbiological attributes of the dosage from should be discussed including the rationale for not performing microbial limits testing for non-sterile products, and the selection and effectiveness of preservatives systems in product containing antimicrobial preservatives. For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed.

P 2.7 Compatibility

The compatibility of the drug product or reconstitution diluents(s) or dosage devices, e.g. precipitation of drug substance in solution, sorption on injection vessels and stability should be addressed to provide appropriate and supportive information for the labeling.

P 3 Manufacture

P 3.1 Batch Formula

The formula with name and quantities of all ingredients (active and otherwise) including substance(s) which are removed in the course of manufacture should be included:

The actual quantities (g, kg, liters) etc. of ingredient should be stated.

Overage: Supporting data and the reason for including the overage shall be enclosed.

The total number of dosage unit per batch must be stated.

A description of all stages involved in the manufacture of the dosage form is required. Reference ICH Guidelines: Biotech: Q6B

P 3.2 Manufacturing Process and Process Control

A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified.

The full description of manufacturing process must sufficient details to cover the essential point of each stage of manufacture.

For sterile product the description includes preparation and sterilization of components. (i.e. Containers, closures, etc).

P 3.3 Controls of Critical Steps and Intermediates

Critical steps: Tests and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps identified P3.3 of the manufacturing process, to ensure that the process is controlled.

Intermediates: information on the quality and control of intermediates isolated during the process should be provided.

Reference ICH Guidelines: Q2A, Q2B, Q6A and Q6B

P 3.4 Process Validation and/or Evaluation

Description, documentation, and result of the validation studies should be provided from critical steps or critical assays used in the manufacturing process. (e.g. Validation of the sterilization process or aseptic processing or filling).

Reference: NCE: Q6B, Biotech: Q6B

P 4 Control of Excipients

P 4.1 Specification

The specification for the excipients should be provided.

Reference ICH Guidelines: NCE: Q6A; Biotech: Q6B

P 4.2 Analytical Procedures

The analytical procedures used for the testing the excipient should be provided, where appropriate.

Reference ICH Guidelines: NCE: Q2A; Biotech: Q6B

P 4.3. Excipients of Human and Animal Origin

For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g. sources, specifications, description of the testing performed, viral safety data).

(Reference ICH Guidelines: NCE: Q5A, Q5D ; Biotech: Q6B)

P 4.4 Novel Excipients

For excipient(s) used for the first time in a drug product or by a new route of administration, full details of manufacture, characterization and controls, with cross references to supporting safety data (nonclinical or clinical) should be provided

P 5 Control of finished Product

Specification and justification of the specification, summary of the analytical procedure and validation, and characterization of impurities.

P 5.1 Specification

The specification for the finished product should be provided.

Reference ICH Guidelines: NCE: Q6A; Biotech: Q6B

-P 5.2 Analytical Procedures.

The analytical procedures use for the testing the finished product should be provided.

Reference ICH Guidelines: NCE: Q2A ; Biotech: Q6B

P 5.3 Validation of Analytical Procedures

Description (including size, origin and use) and test result of all relevant batches e.g. pre-clinical, clinical pilot, scale-up, and if available production-scale batches) used to establish specification and evaluate consistency in manufacturing should be provided.

Reference ICH Guidelines: NCE: Q3A, Q3C, and Q6A; Biotech: Q6B.

Generics: refer to P.3.4.

P 5.4 Batch analyses

Description (including size, origin and use) and test result of all relevant batches e.g. pre-clinical, clinical pilot, scale-up, and if available production-scale batches) used to establish specification and evaluate consistency in manufacturing should be provided.

Reference ICH Guidelines: NCE: Q3A, Q3C, and Q6A; Biotech: Q6B.

Generics: refer to P.3.4.

P 5.5 Characterization of Impurities

P 5.6 Justification of Specification

Justification for the proposed finished product should be provided

Reference ICH Guidelines: NCE: Q3B and Q6A; Biotech: Q6B

P 6 Reference Standards or Materials

Requirement: Quality information and tabulated presentation of Reference standard or materials used for testing of drug product should be included.

Reference: NCE: Q6A, Biotech: Q6B

P 7 Container closure system

A description of the container closure systems should be provided, including the identity of materials of construction of each primary and secondary packaging component, and each specification. The specifications should include description and identification (and critical

dimensions with drawings where appropriate). Non- compendial methods (with validations) should be included where appropriate.

For non-functional secondary packaging components (e.g. those that do not provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

Suitability information should be located in P 2.

P 8 Product Stability

Evidence is required to demonstrate that product is stable, meets the finished product specifications throughout its proposed shelf-life, that toxic decomposition products are not produced in significant amount during this period, and that potency, efficacy of preservative etc. are maintained.

Stability Summary and Conclusion

All criteria under ICH Guidelines are acceptable with the exception of real time storage conditions which should be 300C, 75% RH. Provision of moisture protection of the packaging should be taken into consideration.

Reference ICH Guidelines: Q1A (R2), Q1B, Q2A, Q2B and Q5C

Post-approval stability protocol and stability commitment

The post-approval stability protocol and stability commitment should be provided.

References ICH Guidelines: NCE, Biotech: Q1A (R2) and Q5C

Stability Data

Results of the stability studies should be presented in an appropriate format (e.g. tabular, graphical, narrative). Information on the analytical procedures used to generate the data and validation of these procedures should be included.
Reference: ASEAN Guideline on Stability Study of Drug Product, ASEAN Guideline on Validation of Analytical Procedure

P 9 Product Interchangeability

Not required for NCE

Section H: Key Literature References (Biotech)

Key literature references should be provided, if applicable.

Chapter E Part 2: CTD for Generic Product (Generic)

Scope of the Guideline

Part 2 of the dossier is intended to provide guidance on the format of registration application for drug products regarding CTR. This chapter is appropriate for application of Generic ProductGeneric.

Applicant should first complete dossier requirements Part 1 page 15 above which is general for any type of application.

Depending on the type of applicants for the remaining parts applicant should follow the following cross references

- Dossier requirements for New Chemical Entity go to page 19 Part 2: CTD for New Chemical Entity (NCE)
- Dossier requirements for biotechnological products go to page 31 Part 2: CTD for Biotechnological Product (Biotech)
- Dossier requirements for generic products go to page 43 Part 2: CTD for Generic Product (Generic)
- Dossier requirements for WHO Prequalified products go to page 53 Part 2: CTD for WHO Prequalified Product (WHO-PQP)
- Dossier requirements for products approved by Reference Regulatory Authority go to page 65 Part 2: CTD for Product Approved by Reference Regulatory Authority (RRA)

Part 2: Dossier Requirement (Generic)

Section I: Table of Content

A table of contents for the Generic Product should be provided

Section J: Quality Overall Summary (QOS) (Generic)

The Quality Overall Summary (QOS) is a summary that follows the scope and the outline of the Body of Data in Section C below. The QOS should not include information, data or justification that was not already included in Section C below or in other parts of the common technical document (CTD).

Applicant should complete Quality Overall Summary (QOS) Chapter J page 175 relevant to type of application.

Section K: Body of Data (Generic)

S DRUG SUBSTANCE

S 1 General Information

S 1.1 Nomenclature

- International non–proprietary name (INN)
- Compendial name if relevant
- Registry number of chemical abstract service (CAS)
- Laboratory code (if applicable)
- Chemical name(s)

S 1.2 Structural formula

Compendial requirement or equivalent information from the manufacturer.

S 1.3 General Properties

A list should be provided of physicochemical and other relevant properties of the drug substance.

S 2 Manufacture

S 2.1 Manufacturer(s)

Name and full addresses including the city and country of the manufacturer of active ingredient.

S 2.2 Description of Manufacturing Process and Process Controls

The description of the drug substances manufacturing process represents the applicant's commitment for the manufacture of drug substances.

S 2.3 Control of Materials

Material used in the manufacture of the drug substance (e.g., raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials (including biologically-sourced materials, e.g., media components, monoclonal antibodies, enzymes) meet standards appropriate for their intended use (including the clearance or control of adventitious agents) should be provided, as appropriate. For biologically-sourced materials, this can include information regarding the source, manufacture, and characterization.

S 2.4 Controls of Critical Steps and Intermediates

Critical steps: Tests and acceptance criteria, with justification including experimental data, performed at critical steps of the manufacturing process to ensure that the process is controlled.

Intermediates: Specifications and analytical procedure, if any, for intermediates isolated during the process.

S 2.5 Process Validation and/or Evaluation

Process validation or evaluation studies for aseptic processing and sterilization should be included.

S 2.6 Manufacturing Process Development

S 3 Characterization

S 3.1 Elucidation of Structure and Characteristic

Compendial requirement or equivalent information from the manufacturer should be included.

S 3.2 Impurities

Information on impurities should be provided.

Reference ICH guidelines: Q3A, Q3C, Q5C, Q6A and Q6B

Compendial requirement or equivalent information from the manufacturer should also be included.

S 4 Control of Drug Substance

Specification and justification of specification (s). Summary of analytical procedure and validation.

S 4.1 Specification

Detailed specification, tests and acceptance criteria for the drug substance should be provided.

Reference ICH Guidelines NCE: Q6A

Compendia specification are adequate. Indicate clearly whether the drug substance is purchased based on specification with a certificate of analysis, or tested by applicant.

S 4.2 Analytical Procedures

The analytical procedure used for testing the drug substance should be provided in sufficient detail to enable reproducible testing by another laboratory.

Reference ICH Guidelines: NCE: Q2A ; Biotech: Q6B

Compendial requirement or equivalent information from the manufacturer should also be included.

S 4.3 Validation of Analytical Procedures

This is required for non-compendial method only

Reference ASEAN Guideline for Validation of Analytical Procedure

Analytical validation information, including experimental data for the analytical procedure used for testing the drug substance should be provided. Typical validation characteristics to be considered are selectivity, precision (repeatability, intermediate precision and reproducibility), accuracy, linearity, range, limit of quantitation, limit of detection, robustness, and system suitability.

Reference ICH Guidelines: NCE: Q2A and Q2B; Biotech: Q6B

S 4.4 Batch Analyses

Description of batches and results of batch analyses should be provided

Reference ICH Guidelines: NCE: Q3A, Q3C and Q6A ; Biotech: Q6B

S 4.5 Justification of Specification

Justification for the drug substance specification should be provided.

Reference ICH Guidelines: NCE: Q6A ; Biotech: Q6B

S 5 Reference Standards or Materials

Quality information of Reference standard or material used for testing of substance should be provided.

Reference ICH Guidelines: NCE: Q6A ; Biotech: Q6B

Compendial requirement or equivalent information from the manufacturer should also be provided

S 6 Container Closure System

S 7 Stability

Stability Summary and Conclusion

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate.

Reference ICH Guidelines: Q1A (R2), Q1B, and Q5C

Post-approval Stability Protocol and Stability Commitment

The post-approval stability protocol and stability commitment should be provided.

Reference ICH Guidelines: Q1A (R2) and Q5C

Stability Data

Results of the stability studies (e.g. forced degradation studies and stress conditions) should be

presented in an appropriate format such as tabular, graphical, or narrative. Information on the analytical procedures used to generate the data and validation of these procedures should be included.

Reference ICH Guidelines: Q1A (R2), Q1B, Q2A, Q2B, and Q5C

Manufacturer stability data or equivalent information should also be provided for generic products.

P DRUG PRODUCT (Generic)

P 1 Description and Composition

A description of the drug product and its composition should be provided. The information provided should include, for example:

Description 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 reconstitution diluent(s); and

Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable.

Quantity should be stated in metric weight or measures.

Reference ICH Guidelines: NCE: Q6A ; Biotech: Q6B

P 2 Pharmaceutical Development

P 2.1 Information on Development Studies

P 2.2 Component of Drug Product

P 2.2.1 Active Ingredients

Literature data is sufficient.

P 2.2.2 Excipients

The choice of excipients listed in Item P 1, their concentration and characteristics which influence the drug product performance, should be discussed relative to their respective function.

P 2.3 finished Product

P 2.3.1 formulation Development

A brief summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage. The differences between clinical formulations and the formulation (i.e. Composition) described in Item P 1 and P 2 should be discussed. Results from comparative in vitro studies (e.g. dissolution) or comparative in vivo studies (e.g., bioequivalence) should be discussed when appropriate.

P 2.3.2 Overages

Any overages in the formulation(s) described in Item P 1 should be justified.

P 2.3.3 Physicochemical and biological Properties

Parameters relevant to the performance of the drug product such as pH, ionic strength, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency and immunological activity should be addressed.

P 2.4 Manufacturing Process Development

The selection and optimization of the manufacturing process described in Item P 3.2, in particular its critical aspects, should be explained. Where relevant, the method of sterilization should be explained and justified.

Differences between the manufacturing process(es) used to produce pivotal clinical batches and the process described in Item P 3.2 that can influence the performance of the product should be discussed.

Generics: refer to P.3.2.

P 2.5 Container Closure System

The suitability of the container closure system used for the storage, transportation (shipping) and use of the drug product should be discussed as necessary. This discussion should consider e.g. choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form including sorption to container and leaching safety of materials of contraction, and performance such as reproducibility of the dose delivery from the device when present as part the drug product.

P 2.6 Microbiological Attributes

Where appropriate, the microbiological attributes of the dosage from should be discussed including the rationale for not performing microbial limits testing for non-sterile products, and the selection and effectiveness of preservatives systems in product containing antimicrobial preservatives. For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed.

P 2.7 Compatibility

Literature data are acceptable

P 3 Manufacture

P 3.1 Batch Formula

The formula with name and quantities of all ingredients (active and otherwise) including substance(s) which are removed in the course of manufacture should be included:

The actual quantities (g, kg, liters) etc. of ingredient should be stated.

Overage: Supporting data and the reason for including the overage shall be enclosed.

The total number of dosage unit per batch must be stated.

A description of all stages involved in the manufacture of the dosage form is required. Reference ICH Guidelines: Biotech: Q6B

P 3.2 Manufacturing Process and Process Control

A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified.

The full description of manufacturing process must sufficient details to cover the essential point of each stage of manufacture.

For sterile product the description includes preparation and sterilization of components. (i.e. Containers, closures, etc).

P 3.3 Controls of Critical Steps and Intermediates

Critical steps: Tests and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps identified P3.3 of the manufacturing process, to ensure that the process is controlled.

Intermediates: information on the quality and control of intermediates isolated during the process should be provided.

Reference ICH Guidelines: Q2A, Q2B, Q6A and Q6B

P 3.4 Process Validation and/or Evaluation

ASEAN Guideline on process validation

P 4 Control of Excipients

P 4.1 Specification

Compendial requirements or equivalent information from the manufacturer

P 4.2 Analytical Procedures

Compendial requirements or equivalent information from the manufacturer.

P 4.3. Excipients of Human and Animal Origin

Use compendial requirements if available, otherwise the same requirements apply.

P 4.4 Novel Excipients

For excipient(s) used for the first time in a drug product or by a new route of administration, full details of manufacture, characterization and controls, with cross references to supporting safety data (nonclinical or clinical) should be provided

P 5 Control of finished Product

Specification and justification of the specification, summary of the analytical procedure and validation, and characterization of impurities.

P 5.1 Specification

The specification for the finished product should be provided.

Reference ICH Guidelines: NCE: Q6A; Biotech: Q6B

-P 5.2 Analytical Procedures.

The analytical procedures use for the testing the finished product should be provided.

Reference ICH Guidelines: NCE: Q2A ; Biotech: Q6B

P 5.3 Validation of Analytical Procedures

A tabulated summary of the batch analyses, with graphical representation where appropriate, should be provided.

P 5.4 Batch analyses

A tabulated summary of the batch analyses, with graphical representation where appropriate, should be provided.

P 5.5 Characterization of Impurities

P 5.6 Justification of Specification

Compendial requirements or equivalent information from the manufacture.

P 6 Reference Standards or Materials

Compendial requirements or equivalent information from the manufacture.

P 7 Container closure system

A description of the container closure systems should be provided, including the identity of materials of construction of each primary and secondary packaging component, and each specification. The specifications should include description and identification (and critical dimensions with drawings where appropriate). Non- compendial methods (with validations) should be included where appropriate.

For non-functional secondary packaging components (e.g. those that do not provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

Suitability information should be located in P 2.

P 8 Product Stability

Evidence is required to demonstrate that product is stable, meets the finished product specifications throughout its proposed shelf-life, that toxic decomposition products are not produced in significant amount during this period, and that potency, efficacy of preservative etc. are maintained.

Stability Summary and Conclusion

ASEAN Guideline on Stability Study of Drug Product

Post-approval stability protocol and stability commitment

ASEAN Guideline on Stability Study of Drug Product

Stability Data

Results of the stability studies should be presented in an appropriate format (e.g. tabular, graphical, narrative). Information on the analytical procedures used to generate the data and validation of these procedures should be included.
Reference: ASEAN Guideline on Stability Study of Drug Product, ASEAN Guideline on Validation of Analytical Procedure

P 9 Product Interchangeability

This requirement applies to major variations (MaV) and generic products (G).

The type of studies conducted, protocol used and the result of the studies should be presented in the study report. Type of studies conducted should refer to WHO guidance: Annex 6 Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability in the following link

http://apps.who.int/medicinedocs/en/m/abstract/Js23245en/

Section L: Key Literature References (Generic)

Key literature references should be provided, if applicable.

Non required for Generic

Part 2: CTD for WHO Prequalified Product (WHO-PQP)

Scope of the Guideline

Part 2 of the dossier is intended to provide guidance on the format of registration application for drug products regarding CTR. This chapter is appropriate for application of WHO Prequalified ProductWHO-PQP.

Applicant should first complete dossier requirements Part 1 page 15 above which is general for any type of application.

Depending on the type of applicants for the remaining parts applicant should follow the following cross references

- Dossier requirements for New Chemical Entity go to page 19 Part 2: CTD for New Chemical Entity (NCE)
- Dossier requirements for biotechnological products go to page 31 Part 2: CTD for Biotechnological Product (Biotech)
- Dossier requirements for generic products go to page 43 Part 2: CTD for Generic Product (Generic)
- Dossier requirements for WHO Prequalified products go to page 53 Part 2: CTD for WHO Prequalified Product (WHO-PQP)
- Dossier requirements for products approved by Reference Regulatory Authority go to page 65 Part 2: CTD for Product Approved by Reference Regulatory Authority (RRA)

Part 2: Dossier Requirement (WHO-PQP)

Section M: Table of Content

A table of contents for the WHO Prequalified Product should be provided

Section N: Quality Overall Summary (QOS) (WHO-PQP)

The Quality Overall Summary (QOS) is a summary that follows the scope and the outline of the Body of Data in Section C below. The QOS should not include information, data or justification that was not already included in Section C below or in other parts of the common technical document (CTD).

Applicant should complete Quality Overall Summary (QOS) Chapter J page 175 relevant to type of application.

Section O: Body of Data (WHO-PQP)

S DRUG SUBSTANCE

S 1 General Information

S 1.1 Nomenclature

- International non–proprietary name (INN)
- Compendial name if relevant
- Registry number of chemical abstract service (CAS)
- Laboratory code (if applicable)
- Chemical name(s)

S 1.2 Structural formula

The structural, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided. The applicant should submit information in line with ACTD requirements as submitted to WHO.

S 1.3 General Properties

A list should be provided of physicochemical and other relevant properties of the drug substance. The applicant should submit information in line with ACTD requirements as submitted to WHO.

S 2 Manufacture

S 2.1 Manufacturer(s)

The name and physical addresses of site(s) of the manufacturer for the drug substance should be the same the one inspected and approved by WHO. Applicant is not allowed to include any other manufacturers that have not been approved by WHO. Any new manufacturer, require prior approval by WHO as per WHO variation guidelines before inclusion.

S 2.2 Description of Manufacturing Process and Process Controls

The applicant should submit information in line with ACTD requirements as submitted to WHO. In addition, the method of manufacture for drug substance should be the same as the one approved by WHO.

S 2.3 Control of Materials

The applicant should submit information as submitted to WHO.

That is to say material used in the manufacture of the drug substance (e.g., raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials (including biologically-sourced materials, e.g., media components, monoclonal antibodies, enzymes) meet standards appropriate for their

intended use (including the clearance or control of adventitious agents) should be provided, as appropriate. For biologically-sourced materials, this can include information regarding the source, manufacture, and characterization.

S 2.4 Controls of Critical Steps and Intermediates

The applicant should submit information as submitted to WHO that include the Critical steps: Tests and acceptance criteria, with justification including experimental data, performed at critical steps of the manufacturing process to ensure that the process is controlled.

Intermediates: Specifications and analytical procedure, if any, for intermediates isolated during the process.

S 2.5 Process Validation and/or Evaluation

Process validation or evaluation studies for aseptic processing and sterilization should be included as submitted to WHO.

See also Biotech S.2.5

S 2.6 Manufacturing Process Development

The applicant should submit information in as submitted to WHO.

See also: NCE S.2.6 and Biotech S.2.6

S 3 Characterization

S 3.1 Elucidation of Structure and Characteristic

The applicant should submit information as submitted to WHO.

See also: NCE S.3.1, Biotech S.3.1 and Generic S.3.1

S 3.2 Impurities

Information on impurities should be provided.

Reference ICH guidelines: Q3A, Q3C, Q5C, Q6A and Q6B

The applicant should submit information in as submitted to WHO.

See also: Generic S.3.2

S 4 Control of Drug Substance

Specification and justification of specification (s). Summary of analytical procedure and validation.

S 4.1 Specification

The applicant should submit information in line with ACTD requirements as submitted to

WHO. The quality specification of the drug substance must be the same as the one approved by WHO. Both the drug substance manufacturer and drug product manufacturer should provide release specifications along with their effective date, signed or certified by authorized personnel and reference specification number. The applicant should also provide a declaration that the specifications will remain the same as those approved by WHO. Applicant is not allowed to include any other limits in the specification that have not been approved by WHO. Any new limits in the specification require prior approval by WHO as per WHO variation guidelines before inclusion.

Reference ICH Guidelines NCE: Q6A

See also: Biotech S.4.1 and Generic S.1.

S 4.2 Analytical Procedures

The analytical procedure used for testing the drug substance should be provided in sufficient detail to enable reproducible testing by another laboratory.

Reference ICH Guidelines: NCE: Q2A ; Biotech: Q6B

The analytical methods for testing the drug substance by the drug product manufacturer should be the same as the one approved by WHO. The analytical test procedures along with their effective date, signed or certified by authorized personnel and reference specification number should be provided by the drug product manufacturer. Applicant is not allowed to include any other methods that have not been approved by WHO. Any new methods require prior approval by WHO as per WHO variation guidelines before inclusion.

S 4.3 Validation of Analytical Procedures

The validation of analytical procedures used for testing the drug substance should be the same as the one approved by WHO.

Analytical validation information, including experimental data for the analytical procedure used for testing the drug substance should be provided. Typical validation characteristics to be considered are selectivity, precision (repeatability, intermediate precision and reproducibility), accuracy, linearity, range, limit of quantitation, limit of detection, robustness, and system suitability.

Reference ICH Guidelines: NCE: Q2A and Q2B ; Biotech: Q6B

S 4.4 Batch Analyses

Description of batches and results of batch analyses should be provided

The drug product manufacturer should submit results of at least three batches demonstrating drug substance’s compliance to specifications as approved by WHO.

Reference ICH Guidelines: NCE: Q3A, Q3C and Q6A ; Biotech: Q6B

S 4.5 Justification of Specification

Justification for the drug substance specification should be provided and it has to be the same

as the one submitted to WHO.

Reference ICH Guidelines: NCE: Q6A ; Biotech: Q6B

S 5 Reference Standards or Materials

Quality information of Reference standard or material used for testing of substance should be provided and it has to be the same as the one submitted to WHO.

Reference ICH Guidelines: NCE: Q6A ; Biotech: Q6B

S 6 Container Closure System

The applicant should submit information on container-closure system as submitted to WHO. In addition, the drug product manufacturer should provide information of the container closure system of the drug substance.

See also NCE S.6 and Biotech S.6

S 7 Stability

Stability Summary and Conclusion

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate.

Reference ICH Guidelines: Q1A (R2), Q1B, and Q5C

Post-approval Stability Protocol and Stability Commitment

The post-approval stability protocol and stability commitment should be provided.

Reference ICH Guidelines: Q1A (R2) and Q5C

Stability Data

Results of the stability studies (e.g. forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphical, or narrative. Information on the analytical procedures used to generate the data and validation of these procedures should be included.

Reference ICH Guidelines: Q1A (R2), Q1B, Q2A, Q2B, and Q5C

P DRUG PRODUCT (WHO-PQP)

P 1 Description and Composition

A description of the drug product and its composition should be provided. The information

provided should include, for example:

Description 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 reconstitution diluent(s); and

Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable.

Quantity should be stated in metric weight or measures.

The applicant should also provide a declaration that the qualitative and quantitative of finished drug product will remain the same as those approved by WHO.

Reference ICH Guidelines: NCE: Q6A ; Biotech: Q6B

P 2 Pharmaceutical Development

P 2.1 Information on Development Studies

The applicant should submit information on pharmaceutical development of the finished drug product in line with ACTD requirements as submitted to WHO.

See also NCE P.2.1 and Biotech P.2.1

P 2.2 Component of Drug Product

P 2.2.1 Active Ingredients

The applicant should submit information submitted to WHO.

See NCE P.2.2.1, Biotech P.2.2.1 and Generic P.2.2.1

P 2.2.2 Excipients

The choice of excipients listed in Item P 1, their concentration and characteristics which influence the drug product performance, should be discussed relative to their respective function.

P 2.3 finished Product

P 2.3.1 formulation Development

A brief summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage. The differences between clinical formulations and the formulation (i.e. Composition) described in Item P 1 and P 2 should be discussed. Results from comparative in vitro studies (e.g. dissolution) or comparative in vivo studies (e.g., bioequivalence) should be discussed when appropriate.

The applicant should submit information submitted to WHO.

P 2.3.2 Overages

Any overages in the formulation(s) described in Item P 1 should be justified as submitted to WHO.

P 2.3.3 Physicochemical and biological Properties

Parameters relevant to the performance of the drug product such as pH, ionic strength, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency and immunological activity should be addressed.

The applicant should submit information submitted to WHO.

P 2.4 Manufacturing Process Development

The applicant should submit information submitted to WHO.

The selection and optimization of the manufacturing process described in Item P 3.2, in particular its critical aspects, should be explained. Where relevant, the method of sterilization should be explained and justified.

Differences between the manufacturing process(es) used to produce pivotal clinical batches and the process described in Item P 3.2 that can influence the performance of the product should be discussed.

Generics: refer to P.3.2.

P 2.5 Container Closure System

The applicant should submit information submitted to WHO.

The suitability of the container closure system used for the storage, transportation (shipping) and use of the drug product should be discussed as necessary. This discussion should consider e.g. choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form including sorption to container and leaching safety of materials of contraction, and performance such as reproducibility of the dose delivery from the device when present as part the drug product.

P 2.6 Microbiological Attributes

The applicant should submit information submitted to WHO.

Where appropriate, the microbiological attributes of the dosage from should be discussed including the rationale for not performing microbial limits testing for non-sterile products, and the selection and effectiveness of preservatives systems in product containing antimicrobial preservatives. For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed.

P 2.7 Compatibility

The applicant should submit information submitted to WHO.

The compatibility of the drug product or reconstitution diluents(s) or dosage devices, e.g. precipitation of drug substance in solution, sorption on injection vessels and stability should be addressed to provide appropriate and supportive information for the labeling.

See also Generic P.2.7

P 3 Manufacture

P 3.1 Batch Formula

The formula with name and quantities of all ingredients (active and otherwise) including substance(s) which are removed in the course of manufacture should be included:

The actual quantities (g, kg, liters) etc. of ingredient should be stated.

Overage: Supporting data and the reason for including the overage shall be enclosed.

The total number of dosage unit per batch must be stated.

A description of all stages involved in the manufacture of the dosage form is required. Reference ICH Guidelines: Biotech: Q6B

Any differences in the batch formula from the one approved by WHO should be presented in a tabular format with a comparative discussion of the differences. Any differences require prior approval by WHO as per WHO variation guidelines

P 3.2 Manufacturing Process and Process Control

The applicant should submit information on manufacturing process and process controls of the finished drug product in line with ACTD requirements as submitted to WHO. In addition, the applicant should also provide a declaration that the method of manufacture, manufacturing processes and the process controls used during the manufacture of finished drug product is the same to the one approved by WHO. Applicant is not allowed to include any other method(s) of manufacture, manufacturing processes and the process controls that have not been approved by WHO. Any differences in the method of manufacture, manufacturing processes and the process controls require prior approval by WHO as per WHO variation guidelines.

P 3.3 Controls of Critical Steps and Intermediates

The applicant should submit information of the critical in-process tests and their acceptance criteria performed at the during the manufacturing process of the finished drug product identified in P3.3 in line with ACTD requirements as submitted to WHO.

P 3.4 Process Validation and/or Evaluation

The applicant should submit information on process validation of the finished drug product in line with ACTD requirements as submitted to WHO. In addition, the applicant should submit the latest annual product quality review of the finished drug product to be marketed in the

Kingdom of Cambodia as evidence of continuous manufacturing experience of the prequalified medicine or prequalified vaccine.

P 4 Control of Excipients

P 4.1 Specification

The applicant should submit information on the specification of all excipients used in the finished drug product in line with ACTD requirements as submitted to WHO. In addition, the drug product manufacturer should provide the latest release specifications of all excipients along with their effective date, signed or certified by authorized personnel and reference specification number as approved by WHO. The applicant should also provide a declaration to confirm that the quality specification of all excipients is the same as those approved by WHO. Applicant will not be allowed to include any other excipient specification other those approved by WHO. Any new excipient specification requires prior approval by WHO as per WHO variation guidelines before inclusion.

P 4.2 Analytical Procedures

The applicant should submit information on the analytical methods used for testing each excipient used in the finished drug product in line with ACTD requirements as submitted to WHO.

P 4.3. Excipients of Human and Animal Origin

The applicant should submit information regarding presence of adventitious agents in the excipients sourced from human or animal tissues in line with ACTD requirements as submitted to WHO. In addition, the applicant should also provide a declaration to confirm that the sources of all excipients are the same as those approved by WHO. Applicant will not be allowed to include any other excipient source other those approved by WHO. Any new excipient source requires prior approval by WHO as per WHO variation guidelines before inclusion.

P 4.4 Novel Excipients

The applicant should submit information on novel excipients used in the finished drug product in line with ACTD requirements as submitted to WHO.

P 5 Control of finished Product

P 5.1 Specification

The applicant should submit the latest release and shelf life quality specification of the finished drug product as submitted to WHO. The latest release and shelf life specifications of the finished drug product should be dated, signed or certified by authorized personnel and have an effective date along with their specification reference number. The specification must be the same as the one approved by WHO and be accompanied by a declaration to confirm that the release and shelf life specification of the finished drug product is the same as those approved by WHO. Applicant will neither be allowed to include any other tests in the specification nor change their limits (acceptance criteria) other those approved by WHO. Any new other tests and limits (acceptance criteria) in the specification requires prior approval by WHO as per WHO variation guidelines before inclusion.

-P 5.2 Analytical Procedures.

The analytical test procedures must be the same as the one approved by WHO and be accompanied by a declaration to confirm that the analytical test procedures of the finished drug product are the same as those approved by WHO. Applicant will not be allowed to include any other analytical test procedures other those approved by WHO. Any new other tests and limits (acceptance criteria) in the specification requires prior approval by WHO as per WHO variation guidelines before inclusion.

P 5.3 Validation of Analytical Procedures

The description of batches and results of batch analyses the finished drug product should be provided in line with ACTD requirements. The results submitted should be from at least three batches to demonstrate finished drug product compliance to specifications as approved by WHO.

P 5.4 Batch analyses

The description of batches and results of batch analyses the finished drug product should be provided in line with ACTD requirements. The results submitted should be from at least three batches to demonstrate finished drug product compliance to specifications as approved by WHO.

P 5.5 Characterization of Impurities

P 5.6 Justification of Specification

The applicant should submit information in line with ACTD requirements as submitted to WHO. Any differences in the release and shelf life finished drug product specifications in comparison to the one approved by WHO should be discussed and presented in a comparative table highlighting the differences

P 6 Reference Standards or Materials

The quality information of reference standard or materials used by the drug product manufacturer for testing of substance should be provided in line with ACTD requirements as submitted to WHO.

P 7 Container closure system

The applicant should submit information on container-closure system in line with ACTD requirements as submitted to WHO.

P 8 Product Stability

The applicant should submit information on stability generated as per ACTD requirements and as submitted to WHO. If the data is not in line with ACTD guidelines, the data should be generated afresh, with appropriate discussion. In addition, the storage conditions and shelf life of the finished drug product should be stated.

Stability Data

Results of the stability studies should be presented in an appropriate format (e.g. tabular, graphical, narrative). Information on the analytical procedures used to generate the data and validation of these procedures should be included.
Reference: ASEAN Guideline on Stability Study of Drug Product, ASEAN Guideline on Validation of Analytical Procedure

P 9 Product Interchangeability

For WHO prequalified medicine: The applicant should submit information on the type of studies conducted to confirm the Interchangeability of the finished drug product in line with guidelines for bioavailability and bioequivalence Studies as submitted to WHO.

For WHO prequalified vaccine: Not applicable because this part is not required for vaccines prequalified by WHO.

Section P: Key Literature References (WHO-PQP)

Key literature references should be provided, if applicable.

PART 3: NONCLINICAL DOCUMENT

For WHO prequalified medicine: Not applicable because this part is not required for generic medicines prequalified by WHO.

For WHO prequalified vaccine: The applicant should submit information on the type of studies as submitted to WHO. Reference should be made to WHO guidelines adopted below:

WHO Guidelines on Non-Clinical Evaluation of Vaccines, WHO Technical Report Series No. 927, 2005, or most recent version

Health Canada Guidance Document: Harmonized Requirements for the Licensing of Vaccines and Guidelines for the Preparation of an Application

Part IV: Clinical Document

For WHO prequalified medicine: See section P.9 above on product interchangeability submitted in line with ASEAN guidelines.

For WHO prequalified vaccine: The clinical studies information should be submitted as approved by WHO. The data should follow the format provided by the most up-to-date

version WHO Guidelines on Clinical Evaluation of Vaccines. The WHO recommendations applicable to the specific vaccine should also be considered as well as other national and international regulatory guidelines when submitting this information.

Part V: Post Registration Variation Management

In order to properly manage post-registration variations and avoid situation where post registration variations can be used to change the conditions of a registered prequalified medicine or prequalified vaccine through national procedures, no variations will be allowed for a WHO-prequalified medicine or prequalified vaccine without prior approval from WHO.

Pending Variations: The applicant should provide a list of variations pending and their status in WHO for consideration before registration.

Chapter F Part 2: CTD for Product Approved by Reference Regulatory Authority (RRA)

Scope of the Guideline

Part 2 of the dossier is intended to provide guidance on the format of registration application for drug products regarding CTR. This chapter is appropriate for application of Product Approved by Reference Regulatory AuthorityRRA.

Applicant should first complete dossier requirements Part 1 page 15 above which is general for any type of application.

Depending on the type of applicants for the remaining parts applicant should follow the following cross references

- Dossier requirements for New Chemical Entity go to page 19 Part 2: CTD for New Chemical Entity (NCE)
- Dossier requirements for biotechnological products go to page 31 Part 2: CTD for Biotechnological Product (Biotech)
- Dossier requirements for generic products go to page 43 Part 2: CTD for Generic Product (Generic)
- Dossier requirements for WHO Prequalified products go to page 53 Part 2: CTD for WHO Prequalified Product (WHO-PQP)
- Dossier requirements for products approved by Reference Regulatory Authority go to page 65 Part 2: CTD for Product Approved by Reference Regulatory Authority (RRA)

Part 2: Dossier Requirement (RRA)

Section Q: Table of Content

A table of contents for the Product Approved by Reference Regulatory Authority should be provided

Section R: Quality Overall Summary (QOS) (RRA)

The Quality Overall Summary (QOS) is a summary that follows the scope and the outline of the Body of Data in Section C below. The QOS should not include information, data or justification that was not already included in Section C below or in other parts of the common technical document (CTD).

Applicant should complete Quality Overall Summary (QOS) Chapter J page 175 relevant to type of application.

Section S: Body of Data (RRA)

S DRUG SUBSTANCE

S 1 General Information

S 1.1 Nomenclature

- International non–proprietary name (INN)
- Compendial name if relevant
- Registry number of chemical abstract service (CAS)
- Laboratory code (if applicable)
- Chemical name(s)

S 1.2 Structural formula

The structural, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided.

S 1.3 General Properties

A list should be provided of physicochemical and other relevant properties of the drug substance. The applicant should submit information in line with ACTD requirements.

S 2 Manufacture

S 2.1 Manufacturer(s)

The name and physical addresses of site(s) of manufacture for API should be the same those approved by reference RRA or Accepted by WHO. Applicant are not allowed to include manufacturers different from those not approved by RRA or WHO. Any new manufacturer without CEP or not approved by reference RRA or WHO require prior approval by reference RRA or WHO as per variation guidelines.

S 2.2 Description of Manufacturing Process and Process Controls

The method of manufacture for API should be the same as the one approved by reference regulatory authority and WHO.

S 2.3 Control of Materials

The applicant should submit information as submitted to reference regulatory authority; i.e. material used in the manufacture of the drug substance (e.g., raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials (including biologically-sourced materials, e.g., media components, monoclonal antibodies, enzymes) meet standards appropriate for their intended use (including the clearance or control of adventitious agents) should be provided, as appropriate. For biologically-sourced materials, this can include information regarding the source, manufacture, and characterization.

S 2.4 Controls of Critical Steps and Intermediates

Critical steps: Tests and acceptance criteria, with justification including experimental data, performed at critical steps of the manufacturing process to ensure that the process is controlled.

Intermediates: Specifications and analytical procedure, if any, for intermediates isolated during the process.

S 2.5 Process Validation and/or Evaluation

Process validation or evaluation studies for aseptic processing and sterilization should be included as submitted to reference regulatory authority.

See also Biotech S.2.5

S 2.6 Manufacturing Process Development

The applicant should submit information in as submitted to reference regulatory authority.

See also: NCE S.2.6 and Biotech S.2.6

S 3 Characterization

S 3.1 Elucidation of Structure and Characteristic

The applicant should submit information in as submitted to reference regulatory authority.

See also: NCE S.3.1, Biotech S.3.1 and Generic S.3.1

S 3.2 Impurities

Information on impurities should be provided.

Reference ICH guidelines: Q3A, Q3C, Q5C, Q6A and Q6B

The applicant should submit information in as submitted to reference regulatory authority.

See also: Generic S.3.2

S 4 Control of Drug Substance

Specification and justification of specification (s). Summary of analytical procedure and validation.

S 4.1 Specification

The quality specification of the API must be the same as the one approved by reference regulatory authority and WHO. The FPP Manufacturer should provide release specifications along with their effective date, signed or certified by authorized personnel and reference specification number. The applicant should provide a confirmation that the specifications including all tests and limits are the same as those approved by the reference regulatory authority and WHO..

Reference ICH Guidelines NCE: Q6A

See also: Biotech S.4.1 and Generic S.1.

S 4.2 Analytical Procedures

The analytical procedure used for testing the drug substance should be provided in sufficient detail to enable reproducible testing by another laboratory.

Reference ICH Guidelines: NCE: Q2A ; Biotech: Q6B

The analytical methods for testing the API by the FPP Manufacturer should be the same as the one approved by reference RRA and WHO.

The FPP Manufacturer should provide analytical test procedures along with their effective date, signed or certified by authorized personnel and reference specification number.

S 4.3 Validation of Analytical Procedures

Analytical validation information, including experimental data for the analytical procedure used for testing the drug substance should be provided. Typical validation characteristics to be considered are selectivity, precision (repeatability, intermediate precision and reproducibility), accuracy, linearity, range, limit of quantitation, limit of detection, robustness, and system suitability.

Reference ICH Guidelines: NCE: Q2A and Q2B ; Biotech: Q6B

S 4.4 Batch Analyses

Description of batches and results of batch analyses should be provided

The FPP Manufacturer should submit results from three batches demonstrating compliance to the FPP manufacturer's API specifications as approved by reference RA and WHO.

Reference ICH Guidelines: NCE: Q3A, Q3C and Q6A ; Biotech: Q6B

S 4.5 Justification of Specification

Justification for the drug substance specification should be provided as approved by reference RRA and WHO.

Reference ICH Guidelines: NCE: Q6A ; Biotech: Q6B

S 5 Reference Standards or Materials

Quality information of Reference standard or material used for testing of substance should be provided as approved by reference regulatory authority and WHO.

Reference ICH Guidelines: NCE: Q6A ; Biotech: Q6B

S 6 Container Closure System

The applicant should submit information on container-closure system as approved by reference regulatory authority and WHO. In addition, the drug product manufacturer should provide information of the container closure system of the drug substance.

See also NCE S.6 and Biotech S.6

S 7 Stability

Stability Summary and Conclusion

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate.

Reference ICH Guidelines: Q1A (R2), Q1B, and Q5C

Post-approval Stability Protocol and Stability Commitment

The post-approval stability protocol and stability commitment should be provided.

Reference ICH Guidelines: Q1A (R2) and Q5C

Stability Data

Results of the stability studies (e.g. forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphical, or narrative. Information on the analytical procedures used to generate the data and validation of these procedures should be included.

Reference ICH Guidelines: Q1A (R2), Q1B, Q2A, Q2B, and Q5C

P DRUG PRODUCT (RRA)

P 1 Description and Composition

A description of the drug product and its composition should be provided. The information provided should include, for example:

Description 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 reconstitution diluent(s); and

Type of container and closure used for the dosage form and accompanying reconstitution

diluent, if applicable.

Quantity should be stated in metric weight or measures.

The applicant should provide the description, composition and formulation of the drug product that is the same qualitatively and quantitatively as the one approved by reference regulatory authority and WHO.

Reference ICH Guidelines: NCE: Q6A ; Biotech: Q6B

P 2 Pharmaceutical Development

P 2.1 Information on Development Studies

Applicant should include all information approved by reference regulatory authority or WHO

See also NCE P.2.1 and Biotech P2.1

P 2.2 Component of Drug Product

P 2.2.1 Active Ingredients

Applicant should include all information approved by reference regulatory authority or WHO

See NCE P.2.2.1, Biotech P.2.2.1 and Generic P.2.2.1

P 2.2.2 Excipients

The choice of excipients listed in Item P 1, their concentration and characteristics which influence the drug product performance, should be discussed relative to their respective function.

P 2.3 finished Product

P 2.3.1 formulation Development

A brief summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage. The differences between clinical formulations and the formulation (i.e. Composition) described in Item P 1 and P 2 should be discussed. Results from comparative in vitro studies (e.g. dissolution) or comparative in vivo studies (e.g., bioequivalence) should be discussed when appropriate.

Applicant should include all information approved by reference regulatory authority or WHO

P 2.3.2 Overages

Any overages in the formulation(s) described in Item P 1 should be justified the same as the one approved by reference regulatory authority or WHO

P 2.3.3 Physicochemical and biological Properties

Parameters relevant to the performance of the drug product such as pH, ionic strength,

dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency and immunological activity should be addressed.

Applicant should include all information approved by reference regulatory authority.

P 2.4 Manufacturing Process Development

Applicant should include all information approved by reference regulatory authority.

The selection and optimization of the manufacturing process described in Item P 3.2, in particular its critical aspects, should be explained. Where relevant, the method of sterilization should be explained and justified.

Differences between the manufacturing process(es) used to produce pivotal clinical batches and the process described in Item P 3.2 that can influence the performance of the product should be discussed.

Generics: refer to P.3.2.

P 2.5 Container Closure System

Applicant should include all information approved by reference regulatory authority.

The suitability of the container closure system used for the storage, transportation (shipping) and use of the drug product should be discussed as necessary. This discussion should consider e.g. choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form including sorption to container and leaching safety of materials of contraction, and performance such as reproducibility of the dose delivery from the device when present as part the drug product.

P 2.6 Microbiological Attributes

Applicant should include all information approved by reference regulatory authority.

Where appropriate, the microbiological attributes of the dosage from should be discussed including the rationale for not performing microbial limits testing for non-sterile products, and the selection and effectiveness of preservatives systems in product containing antimicrobial preservatives. For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed.

P 2.7 Compatibility

Applicant should include all information approved by reference regulatory authority.

The compatibility of the drug product or reconstitution diluents(s) or dosage devices, e.g. precipitation of drug substance in solution, sorption on injection vessels and stability should be addressed to provide appropriate and supportive information for the labeling.

See also Generic P.2.7

P 3 Manufacture

P 3.1 Batch Formula

The formula with name and quantities of all ingredients (active and otherwise) including substance(s) which are removed in the course of manufacture should be included:

The actual quantities (g, kg, liters) etc. of ingredient should be stated.

Overage: Supporting data and the reason for including the overage shall be enclosed.

The total number of dosage unit per batch must be stated.

A description of all stages involved in the manufacture of the dosage form is required. Reference ICH Guidelines: Biotech: Q6B

The FPP manufacturer should be the same site(s) of manufacture for FPP as the one approved by RRA. Any additional manufacturers including those used to manufacture intermediates, primary packaging sites and release-testing sites that are not approved by RRA and WHO should not be included.

P 3.2 Manufacturing Process and Process Control

The applicant will be required to submit the last annual product quality review of the product to be marketed in Cambodia as evidence of continuous manufacturing experience if the product. The applicant should submit in a tabular format a comparative discussion of the differences between current submitted formulation in comparison to the one approved by the reference regulatory authority.

P 3.3 Controls of Critical Steps and Intermediates

The applicant should confirm that the method of manufacture, manufacturing processes, control of materials of the FPP is the same to those approved by reference RRA and WHO.

P 3.4 Process Validation and/or Evaluation

P 4 Control of Excipients

P 4.1 Specification

The applicant should confirm that the sources and quality specification of all excipients will remain same as those approved by the reference RRA and WHO. The FPP manufacturer should provide the specification of all excipients as approved by reference RRA and WHO.

P 4.2 Analytical Procedures

The applicant should confirm that the analytical methods used for testing each excipient used is the same to those approved by reference regulatory authority.

P 4.3. Excipients of Human and Animal Origin

Applicant should include all information approved by reference regulatory authority.

See also See NCE P.4.3, Biotech P.4.3 and Generic P.4.3

P 4.4 Novel Excipients

Applicant should include all information approved by reference regulatory authority.

P 5 Control of finished Product

The quality specification of drug product must be the same as the one approved by reference regulatory authority. The applicant should provide release and shelf life specifications and analytical test procedures along with their effective date, signed or certified by authorized personnel and reference specification number.

P 5.1 Specification

The analytical test procedures along with their effective date, signed or certified by authorized personnel and reference specification number.

-P 5.2 Analytical Procedures.

Applicant should include all information approved by reference regulatory authority.

P 5.3 Validation of Analytical Procedures

The drug product manufacturer should submit results from three batches demonstrating compliance to the product manufacturer's specifications.

P 5.4 Batch analyses

The drug product manufacturer should submit results from three batches demonstrating compliance to the product manufacturer's specifications.

P 5.5 Characterization of Impurities

P 5.6 Justification of Specification

Applicant should include all information approved by reference regulatory authority.

P 6 Reference Standards or Materials

Applicant should include all information approved by reference regulatory authority.

P 7 Container closure system

The specifications including descriptions and identification of primary packaging components must be submitted. The details should be same with those provided in stability data generated in ICH Zone IVb.

P 8 Product Stability

The applicant is required to submit stability data approved by reference RRA in addition to data generated at 30±2°C/75±5%RH on production batches of FPP. The data should be

provided in tabulated format, with appropriate discussion as per ASEAN guidelines. In case reference RRA is in different ICH zone as the one for Cambodia the applicant should conduct stability, studies generated in ICH Zone IVb.

Stability Data

Results of the stability studies should be presented in an appropriate format (e.g. tabular, graphical, narrative). Information on the analytical procedures used to generate the data and validation of these procedures should be included.
Reference: ASEAN Guideline on Stability Study of Drug Product, ASEAN Guideline on Validation of Analytical Procedure

P 9 Product Interchangeability

Section T: Key Literature References (RRA)

Key literature references should be provided, if applicable.

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Chapter G Part 3: CTD for Nonclinical Document

Introduction

Part 3 should provide the Nonclinical Overview*, followed by the Nonclinical Written Summaries and the Nonclinical Tabulated Summaries. The document of this part is not required for Generic Products, Minor Variation Products and some Major Variation Products. For ASEAN member countries, the Study Reports of this part may not be required for NCE, Biotechnological Products and other Major Variation Products if the Original Products are already registered and approved for market authorization in Reference Countries[3]. Therefore, the Department of Drug and Food may request necessary documents when deemed necessary.

Section A: Table of Contents

A Table of Contents should be provided that lists all of the nonclinical study reports and gives the location of each study report in the Common Technical Document for the filed application in the following format.

Section B: Nonclinical Overview
1. General Aspect
2. Content and Structural Format

Section C: Nonclinical Written and Tabulated Summaries
1. Nonclinical Written Summaries
   1.1 Introduction
   1.2 General Presentation Issues
2. Content of Nonclinical Written and Tabulated Summaries
   2.1 Pharmacology
      2.1.1 Written Summary
         2.1.1.1 Primary Pharmacodynamics
         2.1.1.2 Secondary Pharmacodynamics
         2.1.1.3 Safety Pharmacology
         2.1.1.4 Pharmacodynamic Drug Interactions
      2.1.2 Tabulated Summary
   2.2 Pharmacokinetics
      2.2.1 Written Summary
         2.2.1.1 Absorption
         2.2.1.2 Distribution
         2.2.1.3 Metabolism
         2.2.1.5 Pharmacokinetic Drug Interaction (Nonclinical)
      2.2.2 Tabulated Summary
   2.3 Toxicology
      2.3.1 Written Summary
         2.3.1.1 Single-Dose Toxicity
         2.3.1.2 Repeat-Dose Toxicity
         2.3.1.3 Genotoxicity
         2.3.1.4 Carcinogenicity

[3] Reference Countries: to be defined by ASEAN member states. *(Marketing +Registered country & Listed)*

* It should be noted that protection of animals in the conduct of nonclinical studies should be taken into consideration to avoid unnecessary use of animals.

2.3.1.5 Reproductive and Developmental Toxicity
2.3.1.5.1 Fertility and Early Embryonic Development
2.3.1.5.2 Embryo-Foetal Development
2.3.1.5.3 Prenatal and Postnatal Development
2.3.1.6 Local Tolerance
2.3.1.7 Other Toxicity Studies (if available)
2.3.2 Tabulated Summary
3. Nonclinical Tabulated Summaries

Section D: Nonclinical Study Reports
1. Table of Contents
2. Pharmacology
2.1 Written Study Reports
2.1.1 Primary Pharmacodynamics
2.1.2 Secondary Pharmacodynamics
2.1.3 Safety Pharmacology
2.1.4 Pharmacodynamic Drug Interactions
3. PHARMACOKINETICS
3.1 Written Study Reports
3.1.1 Analytical Methods and Validation Reports
3.1.2 Absorption
3.1.3 Distribution
3.1.4 Metabolism
3.1.5 Excretion
3.1.6 Pharmacokinetic Drug Interaction (Nonclinical)
3.1.7 Other Pharmacokinetic Studies
4. Toxicology
4.1 Written Study Reports
4.1.1 Single-Dose Toxicity
4.1.2 Repeat-Dose Toxicity
4.1.3 Genotoxicity
4.1.3.1 In-vitro Reports
4.1.3.2 In-vivo Reports
4.1.4 Carcinogenicity
4.1.4.1 Long Term Studies
4.1.4.2 Short or Medium Term Studies
4.1.4.3 Other Studies
4.1.5 Reproductive and Developmental Toxicity
4.1.5.1 Fertility and Early Embryonic Development
4.1.5.2 Embryo-Foetal Development
4.1.5.3 Prenatal and Postnatal Development
4.1.5.4 Studies in which the Offspring Are Dosed and/or Further Evaluated
4.1.6 Local Tolerance
4.1.7 Other Toxicity Studies (if available)
4.1.7.1 Antigenicity
4.1.7.2 Immunotoxicity
4.1.7.3 Dependence
4.1.7.4 Metabolites
4.1.7.5 Impurities
4.1.7.6 Other

Section E: List of Key Literature References
A list of references used, stated in accordance with 1979 "Vancouver Declaration" on "Uniform Requirements for Manuscripts Submitted to Biomedical Journals", or the system used in "Chemical Abstracts", should be provided. Copies of important references cited in the Nonclinical Overview should be provided in this section. All references that have not been provided should be available upon request.

Guide on Nonclinical Overview and Summaries:

This guide provides recommendations for the harmonization of the Nonclinical Overview, Nonclinical Written and Tabulated Summaries.

The primary purpose of nonclinical written and tabulated summaries should be to provide a comprehensive, factual synopsis of the nonclinical data. The interpretation of the data, the clinical relevance of the findings, cross-linking with the quality aspects of the pharmaceutical, and the implications of the nonclinical findings for the safe use of the pharmaceutical (i.e. as applicable to labelling) should be addressed in the nonclinical overview.

Section B: Nonclinical Overview

The nonclinical overview should provide an integrated, overall analysis of the information in the Common Technical Document.

1. General Aspects

The nonclinical overview should present an integrated and critical assessment of the pharmacologic, pharmacokinetic, and toxicologic evaluation of the pharmaceutical. Where relevant guidances on the conduct of studies exist, these should be taken into consideration, and any deviation from these guidances should be discussed and justified. The nonclinical testing strategy should be discussed and justified. There should comment on the good laboratory practice (GLP) status of the studies submitted. Any association between nonclinical findings and the quality characteristics of the human pharmaceutical, the results of clinical trials, or effects seen with related products should be indicated, as appropriate.

Except for biotechnology-derived products, an assessment of the impurities and degradants present in the drug substance and product should be included, along with what is known of their potential pharmacologic and toxicologic effects. This assessment should form part of the justification for proposed impurity limits in the drug substance and product and be appropriately cross- referenced to the quality documentation. The implications of any differences in the chirality, chemical form, and impurity profile between the compound used in the nonclinical studies and the product to be marketed should be discussed. For biotechnology-derived products, comparability of material used in nonclinical and clinical studies and proposed for marketing should be assessed. If a drug product includes a novel excipient, an assessment of the information regarding the excipient's safety should be provided.

Relevant, scientific literature and the properties of related products should be taken into account. If details references to published, scientific literature are to be used in place of studies

conducted by the applicant, this should be supported by an appropriate justification that reviews the design of the studies and any deviations from available guidances. In addition, the availability of information on the quality of batches of drug substances used in these referenced studies should be discussed.

The Nonclinical Overview should contain appropriate reference citations to the Tabulated Summaries in the following format: (Table X.X, Study/Report Number).

2. Content and Structural Format

The Nonclinical Overview should be presented in the following sequence:

Nonclinical Overview

1. Overview of the Nonclinical Testing Strategy
2. Pharmacology
3. Pharmacokinetics
4. Toxicology
5. Integrated Overview and Conclusions
6. List of Literature Citations

Studies conducted to establish the pharmacodynamic effects, the mode of action, and potential side effects should be evaluated, and consideration should be given to the significance of any issues that arise.

The assessment of the pharmacokinetic, toxicokinetic, and metabolism data should address the relevance of the analytical methods used, the pharmacokinetic models, and the derived parameters. It might be appropriate to cross-refer to more detailed consideration of certain issues within the pharmacology or toxicology studies (e.g., impact of the disease states, changes in physiology, antiproduct antibodies, cross-pieces consideration of toxicokinetic data). Inconsistencies in the data should be discussed. Inter- species comparisons of metabolism and systemic exposure comparisons in animals and humans (AUC, Cmax, and other appropriate parameters) should be discussed and the limitations and utility of the nonclinical studies for prediction of potential adverse effects in humans highlighted.

The onset, severity, and duration of the toxic effects, their dose dependency and degree of reversibility (or irreversibility), and species- or gender- related differences should be evaluated and important features discussed, particularly with regard to:

- Pharmacodynamics
- Toxic signs
- Causes of death
- Pathologic findings
- Genotoxic activity ---- the chemical structure of the compound, its mode of action, and its relationship to known genotoxic compounds
- Carcinogenic potential in the context of the chemical structure of the compound, its relationship to known carcinogens, its genotoxic potential, and the exposure data
- Carcinogenic potential in the context of the chemical structure of the compound, its relationship to known carcinogens, its genotoxic potential, and the exposure data
- The carcinogenic risk to humans – if epidemiologic data are available, they should be taken into account
- Fertility, embryofoetal development, pre- and postnatal toxicity

- Studies in juvenile animals
- The consequences of use before and during pregnancy, during lactation, and during paediatric development
- Local tolerance
- Other toxicity studies and/or studies to clarify special problems.

The evaluation of toxicology studies should be arranged in a logical order so that all relevant data elucidating a certain effect and/or phenomenon are brought together. Extrapolation of the data from animals to humans should be considered in relation to:

- Animal species used
- Numbers of animals used
- Routes of administration employed
- Dosages used
- Duration of treatment or of the study
- Systemic exposures in the toxicology species at no observed adverse effect levels and at toxic doses, in relation to the exposures in humans at the maximum recommended human dose. Tables or figures summarising this information are recommended
- The effect of the drug substance observed in nonclinical studies in relation to that expected or observed in humans

If alternatives to whole animal experiments are employed, their scientific validity should be discussed.

The integrated overview and conclusions should clearly define the characteristics of the human pharmaceutical, as demonstrated by the nonclinical studies, and arrive at logical, well-argued conclusions supporting the safety of the product for the intended clinical use. Taking the pharmacology, pharmacokinetics, and toxicology results into account, the implications of the nonclinical findings for the safe human use of the pharmaceutical should be discussed (i.e. as applicable to labelling).

Section C: Nonclinical Written and Tabulated Summaries

1. Guidance on Nonclinical Written Summaries

1.1 Introduction

This guidance is intended to assist authors in the preparation of nonclinical pharmacology, pharmacokinetics and toxicology written summaries in an appropriate format. This guidance is not intended to indicate what studies required. It merely indicates an appropriate format for the nonclinical data that have been acquired.

The sequence and content of the Nonclinical Written Summary sections are described below. It should be emphasised that no guidance can cover all eventualities, and common sense and a clear focus on the needs of the regulatory assessor are the best guides to constructing a document. Therefore, applicants can modify the format, if needed, to provide the best possible presentation of the information and to facilitate the understanding and evaluation of the results.

Whenever appropriate, age- and gender-related effects should be discussed. Relevant findings with stereoisomers and/or metabolites should be included, as appropriate. Consistent use of units throughout the Nonclinical Written Summaries will facilitate their review. A table for converting units might be also useful.

In the Discussion and Conclusion sections, information should be integrated across studies and across species, and exposure in the test animals should be related to exposure in humans given the maximum intended doses

1.2 General Presentation Issues

Order of Presentation of Information Within Sections
When available, in vitro studies should precede in vivo studies. Where multiple studies of the same type are summarized within the

Pharmacokinetics and Toxicology sections, studies should be ordered by species, by route, and then by duration (shortest duration first).

Species should be ordered as follows:
- Mouse
- Rat
- Hamster
- Other rodent
- Rabbit
- Dog
- Nonhuman primate
- Other nonrodent mammal
- Nonmammals

Routes of administration should be ordered as follows:
- The intended route for human use
- Oral
- Intravenous
- Intramuscular
- Intraperitoneal
- Subcutaneous
- Inhalation
- Topical
- Other

Use of Tables and figures
Although the Nonclinical Written Summaries are envisaged to be composed mainly of text, some information contained within them might be more effectively and/or concisely communicated through the use of appropriate tables or figures.

To allow authors flexibility in defining the optimal structure for the written summaries, tables and figures should preferably be included within the text. Alternately, they could be grouped together at the end of each of the Nonclinical Written Summaries.

Throughout the text, reference citations to the Tabulated Summaries should be included in the following format: (Table X.X, Study/Report Number).

Length of Nonclinical Written Summaries
Although there is no formal limit to the length of the Nonclinical Written Summaries, it is recommended that the total length of the three Nonclinical Written Summaries in general not exceed 100-150 pages.

Sequence of Written Summaries and Tabulated Summaries
The following order is recommended:

- Introduction
- Pharmacology written summary
- Pharmacology tabulated summary
- Pharmacokinetics written summary
- Pharmacokinetics tabulated summary
- Toxicology written summary
- Toxicology tabulated summary

2. Content of Nonclinical Written and Tabulated Summaries

Introduction
The aim of this section should be to introduce the reviewer to the pharmaceutical and to its proposed clinical use. The following key elements should be covered:

- Brief information concerning the pharmaceutical's structure (preferably, a structure diagram should be provided) and pharmacologic properties
- Information concerning the pharmaceutical's proposed clinical indication, dose, and duration of use

2.1 Pharmacology

2.1.1 Written Summary

Within the Pharmacology Written Summary, the data should be presented in the following sequence:

- Brief summary
- Primary pharmacodynamics
- Secondary pharmacodynamics
- Safety pharmacology
- Pharmacodynamic drug interactions
- Discussion and conclusions
- Tables and figures (either here or included in text)

Brief Summary
The principal findings from the pharmacology studies should be briefly summarized in approximately two to three pages. This section should begin with a brief description of the content of the pharmacologic data package, pointing out any notable aspects such as the inclusion and/or exclusion of particular data (e.g. lack of an animal model).

2.1.1.1 Primary Pharmacodynamics
Studies on primary pharmcodynamics should be summarized and evaluated. Where possible, it would be helpful to relate the pharmacology of the drug to available data (e.g. selectivity, safety, potency) on other drugs in the class.

2.1.1.2 Secondary Pharmacodynamics
Studies on secondary pharmacodynamics should be summarized by organ system, where

appropriate, and evaluated in this section.

2.1.1.3 Safety Pharmacology

Safety pharmacology studies should be summarized and evaluated in this section. In some cases, secondary pharmacodynamic studies can contribute to the safety evaluation when they predict or assess potential adverse effects in humans. In such cases, these secondary pharmacodynamic studies should be considered, along with safety pharmacology studies.

2.1.1.4 Pharmacodynamic Drug Interactions

If they have been performed, pharmacodynamic drug interaction studies should be briefly summarized in this section.

Discussion and Conclusions

This section provides an opportunity to discuss the pharmacologic evaluation and to consider the significance of any issues that arise.

Tables and figures

Text tables and figures can be included at appropriate points throughout the summary within the text. Alternatively, tables and figures can be included at the end of the summary.

2.1.2 Pharmacology Tabulated Summary (see Annex B:)

The tabulated summary should follow the guidelines in ASEAN Common Technical Dossier (ACTD).

2.2 Pharmacokinetics

2.2.1 Written Summary

The sequence of the Pharmacokinetics Written Summary should be as follows:

- Brief Summary
- Method of analysis
- Absorption
- Distribution
- Metabolism
- Excretion
- Pharmacokinetic drug interactions
- Other pharmacokinetic studies
- Discussion and conclusions
- Tables and figures (either here or included in text)

Brief Summary

The principal findings from the pharmacokinetics studies should be briefly summarized in approximately two or three pages. This section should begin with a description of the scope of the pharmacokinetic evaluation, emphasizing, for example, whether the species and strains examined were those used in the pharmacology ad toxicology evaluations, and whether the formulations used were similar or identical.

Method of Analysis

This section should contain a brief summary of the methods of analysis for biological samples, including the detection and quantification limits of an analytical procedure. If possible, validation data for the analytical method and stability of biological samples should be discussed

in this section. The potential impact of different methods of analysis on the interpretation of the results should be discussed in the following relevant sections.

2.2.1.1 Absorption

The following data should be summarized in this section:

- Absorption (extent and rate of absorption, in vivo and in situ studies)
- Kinetic parameters, bioequivalence and/or bioavailability (serum/plasma/blood PK studies)

2.2.1.2 Distribution

The following data should be summarized in this section

- Tissue distribution studies
- Protein binding and distribution in blood cells
- Placental transfer studies

2.2.1.3 Metabolism (inter-species comparison)

The following data should be summarized in this section:

- Chemical structures and quantities of metabolites in biological samples
- Possible metabolic pathways
- Presystemic metabolism (GI/hepatic first-pass effects)
- In vitro metabolism including P450 studies
- Enzyme induction and inhibition

2.2.1.4 Excretion

The following data should be summarized in this section:

- Routes and extent of excretion
- Excretion in milk

2.2.1.5 Pharmacokinetic Drug Interaction'

If they have been performed, nonclinical pharmacokinetic drug interaction studies (in vitro and/or in vivo) should be briefly summarized in this section.

2.2.1.6 Other Pharmacokinetic Studies

If studies have been performed in nonclinical models of disease (e.g. renally impaired animals), if they should be summarized in this section.

Discussion and Conclusions

This section provides an opportunity to discuss the pharmacokinetic evaluation and to consider the significance of any issues that arise.

Tables and figures

Text tables and figures can be included at appropriate points throughout the summary within the text. Alternatively, there is the option of including tables and figures at the end of the summary.

2.2.2 Pharmacokinetics Tabulated Summary (see Annex B:)

The tabulated summary should follow the guidelines in ASEAN Common Technical Dossier (ACTD).

2.3 Toxicology

2.3.1 Written Summary

The sequence of the Toxicology Written Summary should be as follows:

- Brief summary
- Single-dose toxicity
- Repeat-dose toxicity
- Genotoxicity
- Carcinogenicity
- Reproductive and developmental toxicity
- Studies in juvenile animals
- Local Tolerance
- Other toxicity studies
- Discussion and conclusions
- Tables and figures (either here or included in text)

Brief Summary

The principal findings from the toxicology studies should be briefly summarized in a few pages (generally not more than six). In this section, the extent of the toxicologic evaluation can be indicated by the use of a table listing the principal toxicologic studies (results should not be presented in this table), for example:

Table 3: Quality Overall Toxicology Program

Study type and duration	**Route of administration**	**Species**	**Compound administered***
Single-dose toxicity	Po and iv	Rat and mouse	Parent drug
Single-dose toxicity	Po and iv	Rat and mouse	Metabolite X
Repeat-dose toxicity			
1 month	po	Rat and dog	Parent drug
6 month	po	Rat	Parent drug
9 month	po	Dog	Parent drug

*This column should be included only if metabolites are investigated.

The scope of the toxicologic evaluation should be described in relation to the proposed clinical use. A comment on the GLP status of the studies should be included.

2.3.1.1 Single-dose Toxicity

The single-dose data should be very briefly summarized, in order by species and by route. In some instances, it may be helpful to provide the data in the form of a table.

2.3.1.2 Repeat-Dose Toxicity

Studies should be summarized in order by species, by route, and by duration, giving brief details of the methodology and highlighting important findings (e.g. nature and severity of target organ toxicity, dose (exposure) and/or response relationships, no observed adverse effect levels). Nonpivotal studies can be summarized in less detail (pivotal studies are the definitive

GLP studies specified by ICH guidance M3).

2.3.1.3 Genotoxicity

Studies should briefly summarized in the following order:

- In vitro nonmammalian cell system
- In vitro mammalian cell system
- In vivo mammalian system (including supportive toxicokinetics evaluation)
- Other systems

2.3.1.4 Carcinogenicity (Including supportive toxicokinetics evaluation)

- A brief rationale should explain why the studies were chosen and the basis for high-dose selection. Individual studies should be summarized in the following order:
- Long-term studies (in order by species), including range- finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
- - Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat- dose toxicity or pharmacokinetics)
- Other studies

2.3.1.5 Reproductive and Developmental Toxicity
(including range-finding studies and supportive toxicokinetics evaluations)

Studies should be summarized in the following order, giving brief details of the methodology ad highlighting important findings:

- Fertility and early embryonic development
- Embryofoetal development
- Prenatal and postnatal development, including maternal function
- Studies in which the offspring (juvenile animals) are dosed and/or further evaluated if such studies have been conducted

If modified study designs are used, the subheadings should be modified accordingly.

2.3.1.6 Local tolerance

If local tolerance studies have been performed, they should be summarized in order by species, by route, and by duration, giving brief details of the methodology and highlighting important findings.

2.3.1.7 Other Toxicity Studies (if available)

If other studies have been performed, they should be summarized. When appropriate, the rationale for conducting the studies should be provided.

- Antigenicity
- Immunotoxicity
- Mechanistic studies (if not reported elsewhere)
- Dependence
- Studies on metabolites
- Studies on impurities
- Other studies

Discussion and Conclusions

This section should provide an opportunity to discuss the toxicologic evaluation and the significance of any issues that arise. Tables or figures summarising this information are recommended.

Tables and figures
Text tables and figures can be included at appropriate points throughout the summary within the text. Alternatively, tables and figures can be included at the end of the summary.

2.3.2 Toxicology Tabulated Summary (see Annex B:)
The tabulated summary should follow the guidelines in ASEAN Common Technical Dossier (ACTD).

3. ACTD Guidance on Nonclinical Tabulated Summaries

It is recommended that summary tables for the nonclinical information in the Common Technical Document be provided in the format outlined in ASEAN Common Technical Dossier (ACTD) guidance. Applicants can modify the format, if warranted, to provide the best possible presentation of the information and to facilitate the understanding and evaluation of the results.

The guidance is not intended to indicate what studies are requested, but solely to advise how to tabulate study results if a study is performed.

Applicants can add some items to or delete some items from the ACTD format, where appropriate. One tabular format can contain results from several studies. Alternatively, it may be appropriate to cite the data resulting from one study in several tabular formats.

Section D: Nonclinical Study Reports

For ASEAN member countries, the Study Reports of this part may not be required for NCE, Biotechnological Products and other Major Variation Products if the Original Products are already registered and approved for market authorization in Reference Countries. This guidance presents an agreed upon format for the organization of the nonclinical reports in the Common Technical Document for applications that will be submitted to regulatory authorities. This guidance is not intended to indicate what studies are required. It merely indicates an appropriate format for the nonclinical data that have been acquired.

The appropriate location for individual animal data is in the study report or as an appendix to the study report.

1. Table of Contents
A Table of Contents should be provided that lists all of the Nonclinical Study Reports and gives the location of each study report in the Common Technical Document.

2. Pharmacology
2.1 Written Study Reports
The study reports should be presented in the following order:
2.1.1 Primary Pharmacodynamics
2.1.2 Secondary Pharmacodynamics
2.1.3 Safety Pharmacology
2.1.4 Pharmacodynamic Drug Interactions

3. Pharmacokinetics
3.1 Written Study Reports
The study reports should be presented in the following order:
3.1.1 Analytical Methods and Validation Reports (if separate reports are available)

3.1.2 Absorption
3.1.3 Distribution
3.1.4 Metabolism
3.1.5 Excretion
3.1.6 Pharmacokinetic Drug Interactions (nonclinical)
3.1.7 Other Pharmacokinetic Studies

4. Toxicology

4.1 Written Study Reports

The study reports should be presented in the following order:

4.1.1 Single-Dose Toxicity (in order by species, by route)

4.1.2 Repeat-Dose Toxicity (in order by species, by route, by duration, including supportive toxicokinetics evaluations)

4.1.3 Genotoxicity

4.1.3.1 In vitro

4.1.3.2 In vivo (including supportive toxicokinetics evaluations)

4.1.4 Carcinogenicity (including supportive toxicokinetics evaluations)

4.1.4.1 Long-term studies (in order by species, including range- finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)

4.1.4.2 Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)

4.1.4.3 Other studies

4.1.5 Reproductive and Developmental Toxicity (including range-finding studies and supportive toxicokinetics evaluations) (If modified study designs are used, the following subheadings should be modified accordingly).

4.1.5.1 Fertility and early embryonic development

4.1.5.2 Embryofoetal development

4.1.5.3 Prenatal and postnatal development, including maternal function

4.1.5.4 Studies in which offspring (juvenile animals) are dosed and/or further evaluated

4.1.6 Local Tolerance

4.1.7 Other Toxicity Studies (if available)

4.1.7.1 Antigenicity

4.1.7.2 Immunotoxicity

4.1.7.3 Mechanistic studies (if not included elsewhere)

4.1.7.4 Dependence

4.1.7.5 Metabolites

4.1.7.6 Impurities

4.1.7.7 Other

Section E: List of Key Literature References

CamPORS-CTD Checklist for Product Classification Part 3 Document

(Common Technical Dossier on Nonclinical Data for Pharmaceutical Registration)

Part III: Document	NCE	BIOTECH	MaV			MiV	G
			RT	S/P	IND		
Section A. Table of Content	✓	✓	✓	✓	✓		
Section B. Nonclinical Overview	✓	✓					
1. General Aspect 2. Content and structural format	✓	✓					
Section C. Nonclinical Summary (Written and Tabulated)	✓	✓					
1. Nonclinical Written Summaries							
1.1 Pharmacology							
1.1.1 Primary Pharmacodynamics	✓	✓					
1.1.2 Secondary Pharmacodynamics	✓	✓					
1.1.3 Safety Pharmacology	✓	✓					
1.1.4 Pharmacodynamics Drug Interactions	✓	✓					
1.2 Pharmacokinetics							
1.2.1 Absorption	✓	❖	❖	❖			
1.2.2 Distribution	✓	❖	❖	❖			
1.2.3 Metabolism	✓	❖	❖	❖			
1.2.4 Excretion	✓	❖	❖	❖			
1.2.5 Pharmacokinetics Drug Interaction (non- clinical)	✓						
1.2.6 Other Pharmacokinetics Studies	✓		❖				
1.3 Toxicology							
1.3.1 Single dose toxicity	✓	✓					
1.3.2 Repeat dose toxicity	✓	✓					
1.3.3 Genotoxicity	✓						
1.3.4 Carcinogenicity	✓	♦					
1.3.5 Reproductive and developmental toxicity	✓	✓					
1.3.5.1 Fertility and early	✓	✓					

Part III: Document	NCE	BIOTECH	MaV			MiV	G
			RT	S/P	IND		
embryonic development							
1.3.5.2 Embryo-fetal development	✓	✓					
1.3.5.3 Prenatal and postnatal development	✓	✓					
1.3.6 Local tolerance	❖	❖	❖	❖	❖		
1.3.7 Other toxicity studies, if available	❖	❖	❖	❖	❖		
2. Nonclinical Tabulated Summaries	✓	✓	❖	❖	❖		
Section D. Nonclinical Study Report (As requested)							
1. Table of Content	✓	✓					
2. Pharmacology							
2.1 Primary Pharmacodynamics	✓	✓					
2.2 Secondary Pharmacodynamics	✓	✓					
2.3 Safety Pharmacology	✓	✓					
2.4 Pharmacodynamics Drug Interactions	✓	✓					
3. Pharmacokinetics							
3.1 Analytical Methods and Validation Reports	✓	❖					
3.2 Absorption	✓	❖	❖	❖			
3.3 Distribution	✓	❖	❖	❖			
3.4 Metabolism	✓	❖	❖	❖			
3.5 Excretion	✓	❖	❖	❖			
3.6 Pharmacokinetics Drug Interaction (non- clinical)	✓	❖					
3.7 Other Pharmacokinetics studies	✓	❖	❖				
4. Toxicology							
4.1 Single dose toxicity	✓	✓					
4.2 Repeat dose toxicity	✓	✓					
4.3 Genotoxicity	✓						
4.3.1 In vitro	✓						
4.3.2 In vivo	✓						

Part III: Document	NCE	BIOTECH	MaV			MiV	G
			RT	S/P	IND		
4.4 Carcinogenicity	✓	♦					
4.4.1 Long term studies	✓	♦					
4.4.2 Short- or medium-term studies	✓	♦					
4.4.3 Other studies	✓	♦					
4.5 Reproductive and developmental toxicity	✓	✓					
4.5.1 Fertility and early embryonic development	✓	✓					
4.5.2 Embryo-fetal development	✓	✓					
4.5.3 Prenatal and postnatal development	✓	✓					
4.5.4 Studies in which the offspring are dosed and/or further evaluated	✓	✓					
4.6 Local tolerance	❖	❖	❖	❖	❖		
4.7 Other toxicity studies, if available	❖	❖	❖	❖	❖		
4.7.1 Antigenicity							
4.7.2 Immunotoxicity							
4.7.3 Dependence							
4.7.4 Metabolites							
4.7.5 Impurities							
4.7.6 Other							
Section E. List of Key Literature References	✓	✓	❖	❖	❖		

Key

NCE - New chemical entity
Biotech - Biotechnology-derived product
MaV - Major variation (Pharmaceutical product that has undergone variation affecting one or more of the following: the route of administration, strength and posology, indications. The submission of additional data is required and necessary to establish the quality, safety and efficacy of the new formulation resulting from the variation)
RT - Route of administration
S / P - Strength and Posology
IND - Indication
MiV - Minor Variation (Pharmaceutical product that has undergone variation affecting one or more of the following: route of administration, strength and posology, indications or active ingredient/s. The submission of additional data is required and necessary to establish the quality of the new formulation

resulting from the variation)

G - Generic product

❖ - Where applicable, i.e. change of route of administration due to change in formulation

⧫ - Generally inappropriate for biotechnology-derived products, however, product-specific assessment of carcinogenic potential may be needed depending upon duration of clinical dosing, patient population and /or biological activity of the product (e.g. Growth factors, immunosuppressive agents, etc.

Chapter H Part 4: CTD for Clinical Document

Part 4: Clinical Document

Section A: Table of Contents

A table of contents for the filed application should be provided.

Section B: Clinical Overview Preamble

The Clinical Overview is intended to provide a critical analysis of the clinical data in the Common Technical Dossier (CTD). The Clinical Overview is primarily intended for use by DDF in the review of the clinical section of a marketing application. The Clinical Overview should present the strengths and limitations of the development program and study results, analyze the benefits and risks of the medicinal product in its intended use, and describe how the study results support critical parts of the prescribing information.

In order to achieve these objectives, the Clinical Overview should:

- describe and explain the overall approach to the clinical development of a medicinal product, including critical study design decisions.
- assess the quality of the design and performance of the studies, and include a statement regarding GCP compliance.
- provide a brief overview of the clinical findings, including important limitations (e.g., lack of comparisons with an especially relevant active comparator, or absence of information on some patient populations, on pertinent endpoints, or on use in combination therapy).
- provide an evaluation of benefits and risks based upon the conclusions of the relevant clinical studies, including interpretation of how the efficacy and safety findings support the proposed dose and target indication and an evaluation of how prescribing information and other approaches will optimize benefits and manage risks.
- address particular efficacy or safety issues encountered in development, and how they have been evaluated and resolved.
- explore unresolved issues, explain why they should not be considered as barriers to approval, and describe plans to resolve them.
- explain the basis for important or unusual aspects of the prescribing information.

The Clinical Overview should generally be a relatively short document (about 30 pages). The length, however, will depend on the complexity of the application. The use of graphs and concise tables in the body of the text is encouraged for brevity and to facilitate understanding. It is not intended that material presented fully elsewhere be repeated in the Clinical Overview; cross-referencing to more detailed presentations provided in the Clinical Summary or Clinical Study Reports are encouraged.

Detailed Discussion of Content of the Clinical Overview Section

1. Product Development Rationale

The discussion of the rationale for the development of the medicinal product should:

- identify the pharmacological class of the medicinal product.
- describe the particular clinical/pathophysiological condition that the medicinal product

is intended to treat, prevent, or diagnose (the targeted indication).
- briefly summarize the scientific background that supported the investigation of the medicinal product for the indication(s) that was (were) studied.
- briefly describe the clinical development programme of the medicinal product, including ongoing and planned clinical studies and the basis for the decision to submit the application at this point in the programme.
- note and explain concordance or lack of concordance with current standard research approaches regarding the design, conduct and analysis of the studies. Pertinent published literature should be referenced

2. Overview of biopharmaceutics

The purpose of this section is to present a critical analysis of any important issues related to bioavailability that might affect efficacy and/or safety of the to-be-marketed formulation(s) (e.g., dosage form/strength proportionality, differences between the to- be-marketed formulation and the formulation(s) used in clinical trials, and influence of food on exposure).

3. Overview of Clinical Pharmacology

The purpose of this section is to present a critical analysis of the pharmacokinetic (PK), pharmacodynamic (PD), and related in vitro data in the ACTD. The analysis should consider all relevant data and explain why and how the data support the conclusions drawn. It should emphasize unusual results and known or potential problems, or note the lack thereof. This section should address:

- pharmacokinetics, e.g., comparative PK in healthy subjects, patients, and special populations; PK related to intrinsic factors (e.g., age, sex, race, renal and hepatic impairment) and to extrinsic factors (e.g., smoking, concomitant drugs, diet); rate and extent of absorption; distribution, including binding with plasma proteins; specific metabolic pathways, including effects of possible genetic polymorphism and the formation of active and inactive metabolites; excretion; time-dependent changes in pharmacokinetics; stereochemistry issues; clinically relevant PK interactions with other medicinal products or other substances.
- pharmacodynamics, e.g., information on mechanism of action, such as receptor binding; onset and/or offset of action; relationship of favorable and unfavorable pharmacodynamic effects to dose or plasma concentration (i.e., PK/PD relationships); PD support for the proposed dose and dosing interval; clinically relevant PD interactions with other medicinal products or substances; and possible genetic differences in response.
- interpretation of the results and implications of immunogenicity studies, clinical microbiology studies, or other drug class specific PD studies.

4. Overview of Efficacy

The purpose of this section is to present a critical analysis of the clinical data pertinent to the efficacy of the medicinal product in the intended population. The analysis should consider all relevant data, whether positive or negative, and should explain why and how the data support the proposed indication and prescribing information. Those studies deemed relevant for evaluation of efficacy should be identified, and reasons that any apparently adequate and well-controlled studies are not considered relevant should be provided. Prematurely terminated studies should be noted and their impact considered. The following issues should generally be considered:

- relevant features of the patient populations, including demographic features, disease stage, any other potentially important covariates, any important patient populations excluded from critical studies, and participation of children and elderly (ICH E11 and E7). Differences between the studied population(s) and the population that would be expected to receive the medicinal product after marketing should be discussed.
- implications of the study design(s), including selection of patients, duration of studies and choice of endpoints and control group(s). Particular attention should be given to endpoints for which there is limited experience. Use of surrogate endpoints should be justified. Validation of any scales used should be discussed.
- for non-inferiority trials used to demonstrate efficacy, the evidence supporting a determination that the trial had assay sensitivity and justifying the choice of non-inferiority margin (ICH E10).
- statistical methods and any issues that could affect the interpretation of the study results (e.g., important modifications to the study design, including endpoint assessments and planned analyses, as they were specified in the original protocol; support for any unplanned analyses; procedures for handling missing data; and corrections for multiple endpoints).
- similarities and differences in results among studies, or in different patient sub- groups within studies, and their effect upon the interpretation of the efficacy data.
- observed relationships between efficacy, dose, and dosage regimen for each indication, in both the overall population and in the different patient subgroups (ICH E4).
- for products intended for long-term use, efficacy findings pertinent to the maintenance of long-term efficacy and the establishment of long-term dosage. Development of tolerance should be considered.
- data suggesting that treatment results can be improved through plasma concentration monitoring, if any, and documentation for an optimal plasma concentration range.
- the clinical relevance of the magnitude of the observed effects.
- if surrogate endpoints are relied upon, the nature and magnitude of expected clinical benefit and the basis for these expectations.
- efficacy in special populations. If efficacy is claimed with inadequate clinical data in the population, support should be provided for extrapolating efficacy from effects in the general population.

5. Overview of Safety

The purpose of this section is to provide a concise critical analysis of the safety data, noting how results support and justify proposed prescribing information. A critical analysis of safety should consider:

- adverse effects characteristic of the pharmacological class. Approaches taken to monitor for similar effects should be described.
- special approaches to monitoring for particular adverse events (e.g., ophthalmic, QT interval prolongation).
- relevant animal toxicology and product quality information. Findings that affect or could affect the evaluation of safety in clinical use should be considered.
- the nature of the patient population and the extent of exposure, both for test drug and control treatments. Limitations of the safety database, e.g., related to inclusion/exclusion criteria and study subject demographics, should be considered, and the implications of such limitations with respect to predicting the safety of the product in the marketplace should be explicitly discussed.
- common and non-serious adverse events, with reference to the tabular presentations of

events with the test drug and with control agents in the Clinical Summary. The discussion should be brief, focusing on events of relatively high frequency, those with an incidence higher than placebo, and those that are known to occur in active controls or other members of the therapeutic class. Events that are substantially more or less common or problematic (considering the duration and degree of the observed events) with the test drug than with active controls are of particular interest.

- serious adverse events (relevant tabulations should be cross-referenced from the Clinical Summary). This section should discuss the absolute number and frequency of serious adverse events, including deaths, and other significant adverse events (e.g., events leading to discontinuation or dose modification), and should discuss the results obtained for test drug versus control treatments. Any conclusions regarding causal relationship (or lack of this) to the product should be provided. Laboratory findings reflecting actual or possible serious medical effects should be considered.
- similarities and differences in results among studies, and their effect
- upon the interpretation of the safety data.
- any differences in rates of adverse events in population subgroups, such as those defined by demographic factors, weight, concomitant illness, concomitant therapy, or polymorphic metabolism.
- relation of adverse events to dose, dose regimen, and treatment duration.
- long-term safety (E1a).
- methods to prevent, mitigate, or manage adverse events.
- reactions due to overdose; the potential for dependence, rebound phenomena and abuse, or lack of data on these issues.
- world-wide marketing experience. The following should be briefly discussed:
  - the extent of the world-wide experience,
  - any new or different safety issues identified,
  - any regulatory actions related to safety.

6. Benefits and Risks Conclusions

The purpose of this section is to integrate all of the conclusions reached in the previous sections about the biopharmaceutics, clinical pharmacology, efficacy and safety of the medicinal product and to provide an overall appraisal of the benefits and risks of its use in clinical practice. Also, implications of any deviations from regulatory advice or guidelines and any important limitations of the available data should be discussed here. This assessment should address critical aspects of the proposed Prescribing Information. This section should also consider the risks and benefits of the medicinal product as they compare to available alternative treatments or to no treatment in illnesses where no treatment may be a medically acceptable option; and should clarify the expected place of the medicinal product in the armamentarium of treatments for the proposed indication. If there are risks to individuals other than those who will receive the drug, these risks should be discussed (e.g., risks of emergence of drug-resistant bacterial strains with widespread use of an antibiotic for minor illnesses). The analyses provided in previous sections should not be reiterated here. This section often can be quite abbreviated when no special concerns have arisen and the drug is a member of a familiar pharmacological class.

This analysis of benefits and risks is generally expected to be very brief but it should identify the most important conclusions and issues concerning each of the following points:

- the efficacy of the medicinal product for each proposed indication.
- significant safety findings and any measures that may enhance safety.

- dose-response and dose-toxicity relationships; optimal dose ranges and dosage regimens.
- efficacy and safety in sub-populations, e.g., those defined by age, sex, ethnicity, organ function, disease severity, and genetic polymorphisms.
- data in children in different age groups, if applicable, and any plans for a development programme in children.
- any risks to the patient of known and potential interactions, including food-drug and drug-drug interactions, and recommendations for product use.
- any potential effect of the medicinal product that might affect ability to drive or operate heavy machinery.
- Examples of issues and concerns that could warrant a more detailed discussion of benefits and risks might include:
- the drug is for treatment of a non-fatal disease but has known or potential serious toxicity, such as a strong signal of carcinogenicity, teratogenicity, pro-arrhythmic potential (effect on QT interval), or suggestion of hepatotoxicity.
- the proposed use is based on a surrogate endpoint and there is a well-documented important toxicity.
- safe and/or effective use of the drug requires potentially difficult selection or management approaches that require special physician expertise or patient training.

Section C: Clinical Summary

Preamble

The document of this part is not required for Generic Products, Minor Variation Products and some Major Variation Products. For ASEAN member countries, the Clinical Study Reports of this part may not be required for NCE, Biotechnological Products and other Major Variation Products if the Original Products are already registered and approved for market authorization in Reference Countries. Therefore, the Department of Drug and Food may request for additional documentation on Clinical Study Reports when deemed necessary.

The Clinical Summary is intended to provide a detailed, factual summarization of all of the clinical information in the Common Technical Dossier (CTD). This includes information provided in Clinical Study Reports; information obtained from any meta- analyses or other cross-study analyses for which full reports have been included in Clinical Study Reports and post-marketing data for products that have been marketed in other regions. The comparisons and analyses of results across studies provided in this document should focus on factual observations. In contrast, the CTD Clinical Overview document should provide critical analysis of the clinical study program and its results, including discussion and interpretation of the clinical findings and discussion of the place of the test drug in the armamentarium.

The length of the Clinical Summary will vary substantially according to the information to be conveyed, but it is anticipated that (excluding attached tables) the Clinical Summary will usually be in the range of 50 to 400 pages.

Detailed Guidance on Items of the Clinical Summary

1. Summary of Biopharmaceutic Studies and Associated Analytical Methods

1.1 Background and Overview

This section should provide the reviewer with an overall view of the formulation development process, the in vitro and in vivo dosage form performance, and the general approach and rationale used in developing the bioavailability (BA), comparative BA, bioequivalence (BE), and in vitro dissolution profile database. Reference should be made to any guidelines or literature used in planning and conducting the studies. This section should also provide the reviewer with an overview of the analytical methods used, with emphasis on the performance characteristics of assay validation (e.g., linearity range, sensitivity, specificity) and quality control (e.g., accuracy and precision). This section should not include detailed information about individual studies.

1.2 Summary of Results of Individual Studies

A tabular listing of all biopharmaceutic studies should generally be provided, together with narrative descriptions of relevant features and outcomes of each of the individual studies that provided important in vitro or in vivo data and information relevant to BA and BE. The narrative descriptions should be brief, e.g., similar to an abstract for a journal article, and should describe critical design features and critical results. Similar studies may be described together, noting the individual study results and any important differences among the studies. These narratives may be abstracted from the ICH E3 synopsis. References or electronic links to the full report of each study should be included in the narratives.

1.3 Comparison and Analyses of Results across Studies

This section should provide a factual summary of all in vitro dissolution, BA, and comparative BA studies carried out with the drug substance

or drug product, with particular attention to differences in results across studies. This overview should typically summarize the findings in text and tables and should consider the following:

- evidence of the effects of formulation and manufacturing changes on in vitro dissolution and BA and conclusions regarding BE. When manufacturing or formulation changes are made for products containing complex drug substances (e.g., a protein), pharmacokinetic (PK) studies comparing the product before and after the changes may be performed to ensure that the PK characteristics have not changed as a result of product changes. Although such studies are sometimes referred to as BE studies, they generally do not focus on assessing release of drug substance from drug product. Nonetheless, such studies should be reported in this section. Note also that PK studies alone may not be sufficient to assure similarity between such drug products. In many situations, pharmacodynamic (PD) studies or clinical trials may be necessary. Additionally, depending on the circumstances, antigenicity data may also be needed. Results of these other types of studies, when they are needed, should be reported in the appropriate places in the dossier.
- evidence of the extent of food effects on BA and conclusions regarding BE with respect to meal type or timing of the meal (where appropriate).

- evidence of correlations between in vitro dissolution and BA, including the effects of pH on dissolution, and conclusions regarding dissolution specifications.
- comparative bioavailability, including BE conclusions, for different dosage form strengths.
- comparative BA of the clinical study formulations (for clinical studies providing substantial evidence of efficacy) and the formulations to be marketed.
- the source and magnitude of observed inter- and intra-subject variability for each formulation in a comparative BA study.

Tables and figures should be embedded in the text of the appropriate sections when they enhance the readability of the document. Follow the ACTD format and examples to develop such tables.

2. Summary of Clinical Pharmacology Studies

2.1 Background and Overview

This section should provide the reviewer with an overall view of the clinical pharmacology studies. These studies include clinical studies performed to evaluate human pharmacokinetics (PK), and pharmacodynamics (PD), and in vitro studies performed with human cells, tissues, or related materials (hereinafter referred to as human biomaterials) that are pertinent to PK processes. For vaccine products, this section should provide the reviewer with immune response data that support the selection of dose, dosage schedule, and formulation of the final product. Where appropriate, relevant data that are summarized in Items 1, 3 and 4 of Section C can also be referenced to provide a comprehensive view of the approach and rationale for the development of the pharmacokinetic, pharmacodynamic, PK/PD and human biomaterial database. This section should not include detailed information about individual studies. This section should begin with a brief overview of the human biomaterial studies that were conducted and that were intended to help in the interpretation of PK or PD data. Studies of permeability (e.g., intestinal absorption, blood brain barrier passage), protein binding, hepatic metabolism, and metabolic-based drug-drug interactions are particularly relevant. This should be followed by a brief overview of the clinical studies that were carried out to characterize PK and PD of the medicinal product, including studies of PK/PD relationships in healthy subjects and patients. Critical aspects of study design and data analysis should be noted, e.g., the choice of the single or multiple doses used, the study population, the choice of PD endpoints, and whether a traditional approach or a population approach was used to collect and analyze data to assess PK or PD.

2.2 Summary of Results of Individual Studies

A tabular listing of all clinical pharmacology studies should generally be provided together with a narrative description of the relevant features and outcomes of each of the critical individual studies that provided in vitro or in vivo data and information relevant to PK, PD and PK/PD relationships. The narrative descriptions should be brief, e.g., similar to an abstract for a journal article, and should describe critical design features and critical results. Similar studies may be described together, noting the individual study results and any important differences among the studies. References or electronic links to the full report of each study should be included in the narratives.

Summaries of dose-response or concentration response (PK/ PD) studies with pharmacodynamic endpoints should generally be included in this section. In some cases,

however, when well-controlled dose-response PD or PK/PD studies provide important evidence of efficacy or safety, they should be placed in Item 3 or 4 as appropriate and referenced, but not summarized, here.

2.3 Comparison and Analyses of Results across Studies

This section should use the results of all in vitro human biomaterial studies and PK, PD and PK/PD studies to characterize the PK, PD and PK/PD relationships of the drug. Results related to the inter- and intra- individual variability in these data affecting these pharmacokinetic relationships should be discussed.

This section (typically with the use of text and tables) should provide a factual presentation of all data across studies pertinent to the following:

- in vitro drug metabolism and in vitro drug-drug interaction studies and their clinical implications.
- human PK studies, including the best estimates of standard parameters and sources of variability. The focus should be on evidence supporting dose and dose individualization in the target patient population and in special populations, e.g., pediatric or geriatric patients, or patients with renal or hepatic impairment.
- comparison between single and repeated-dose PK
- population PK analyses, such as results based on sparse sampling across studies that address inter-individual variations in the PK or PD of the active drug substances.
- dose-response or concentration-response relationships. This discussion should highlight evidence to support the selection of dosages and dose intervals studied in the important clinical trials. In addition, information that supports the dosage instructions in the proposed labelling should be discussed in Item 3.4.
- major inconsistencies in the human biomaterial, PK, or PD database.

2.4 Special Studies

This section should include studies that provide special types of data relevant to specific types of medicinal products. For immunogenicity studies and other studies in which data may correlate with PK, PD, safety, and/or efficacy data, explanations of such correlations should be summarized here. Any observed or potential effects on PK, PD, safety and/or efficacy should be considered in other appropriate sections of the Clinical Summary as well, with cross-referencing to this section. Human studies that address a specific safety issue should not be reported here, but instead should be reported in Item 4, Summary of Clinical Safety. Follow the ATCD guidance.

Example 1: Immunogenicity

For protein products and other products to which specific immunological reactions have been measured, data regarding immunogenicity should be summarized in this section. For vaccines or other products intended to induce specific immune reactions, immunogenicity data should be described in the efficacy section. Assays used should be briefly described and information about their performance (e.g., sensitivity, specificity, reliability, validity) should be summarized; the location in the application of detailed information should be cross-referenced.

Data regarding the incidence, titre (titer), timing of onset and duration of antibody responses should be summarized for each type of antibody assay used (e.g., IgG by ELISA,

neutralization). Relationships of antibody formation to underlying disease, concomitant medication, dose, duration, regimen, and formulation should be explored and summarized. For drugs intended to be given as chronic, continuous therapy, any data on the impact of interruptions of therapy on antigenicity should be analyzed and summarized.

It is particularly important to summarize analyses of potential clinically relevant correlates of immunogenicity, e.g., to determine the extent to which the presence of antibodies of a particular type or titer appears to correlate with alterations of PK, changes in PD, loss of efficacy, loss of adverse event profile, or development of adverse events. Particular attention should be paid to events that might be immunologically mediated (e.g., serum sickness) and events that might result from binding of cross- reactive endogenous substances by antibodies to the administered drug.

Example 2: Clinical microbiology

For antimicrobial or antiviral medicinal products, in vitro studies to characterize the spectrum of activity are an important part of the program of studies relevant to clinical efficacy. Clinical efficacy studies that include characterization of the susceptibility of the clinical isolates as a part of the efficacy determination should be included in Item 3, Summary of Clinical Efficacy. However, studies that evaluate such findings as the pattern of in vitro susceptibility of strains of bacteria from different parts of the world (not in the context of clinical efficacy study) would be included here.

3. Summary of Clinical Efficacy

There might be time when a product may be effective for more than one indication, then a separate Section 3 should be provided for each indication, although closely related indications can be considered together. When more than one Section 3 is submitted, the sections should be labelled 3A, 3B, 3C, etc.

3.1 Background and Overview of Clinical Efficacy

This section should describe the program of controlled studies and other pertinent studies in the application that evaluated efficacy specific to the indication(s) sought.

Any results of these studies that are pertinent to evaluation of safety should be discussed in Item 4, Summary of Clinical Safety.

The section should begin with a brief overview of the design of the controlled studies that were conducted to evaluate efficacy. These studies include dose-response, comparative efficacy, long-term efficacy, and efficacy studies in population subsets. Critical features of study design should be discussed, e.g., randomization, blinding, choices of control treatment, choice of patient population, unusual design features such as crossover or randomized withdrawal designs, use of run-in periods, other methods of "enrichment", study endpoints, study duration, and prespecified plans for analysis of the study results. Although this section is intended to focus on clinical investigations, nonclinical data and clinical pharmacology data may also be referenced as appropriate to provide a comprehensive summary of human experience related to efficacy. This section should not include detailed information about individual studies.

3.2 Summary of Results of Individual Studies

A tabular listing of all studies that provided (or were designed to provide) information relevant to product efficacy should generally be provided, together with narrative descriptions for important studies. The narrative descriptions should be brief, e.g., similar to an abstract for a journal article, and should describe critical design features and critical results. Similar studies may be described together, noting the individual study results and any important differences among the studies. For studies that also contributed significantly to the safety analysis, study narratives should include information about the extent of exposure of study subjects to the test drug or control agent, and how safety data were collected. These narratives can be abstracted from the synopses of the clinical study reports (ICH E3). References or electronic links to the full report of each study should be included in the narratives.

3.3 Comparison and Analyses of Results across Studies

Using text, figures, and tables as appropriate, the Item of 3.3 should summarize all available data that characterize the efficacy of the drug. This summary should include analyses of all data, irrespective of their support for the overall conclusion and should, therefore, discuss the extent to which the results of the relevant studies do or do not reinforce each other. Any major inconsistencies in the data regarding efficacy should be addressed and any areas needing further exploration should be identified.

The section will generally utilize two kinds of analyses: comparison of results of individual studies, and analysis of data combined from various studies. Details of analyses that are too extensive to be reported in a summary document should be presented in a separate report, to be placed in Clinical Study Reports.

This section should also cross-reference important evidence from Item 2, such as data that support the dosage and administration section of the labelling. These data include dosage and dose interval recommended, evidence pertinent to individualization of dosage and need for modifications of dosage for specific subgroups (e.g., pediatric or geriatric subjects, or subjects with hepatic or renal impairment), and data relevant to dose-response or concentration response (PK/PD) relationships.

3.3.1 Study Populations

The demographic and other baseline characteristics of patients across all efficacy studies should be described. The following should be included:

- the characteristics of the disease (e.g., severity, duration) and prior treatment in the study subjects, and study inclusion/exclusion criteria
- differences in baseline characteristics of the study populations in different studies or groups of studies.
- any differences between populations included in critical efficacy analyses and the overall patient population that would be expected to receive the drug when it is marketed should be noted.
- assessment of the number of patients who dropped out of the studies, time of withdrawal (a defined study day or visit during treatment or follow up period), and reasons for discontinuation.

Tabular presentations that combine and compare study populations across studies may be useful.

3.3.2 Comparison of Efficacy Results of all Studies

The results from all studies designed to evaluate the drug's efficacy should be summarized and compared, including studies with inconclusive or negative results. Important differences in study design such as endpoints, control group, study duration, statistical methods, patient population, and dose should be identified.

Comparisons of results across studies should focus on pre- specified primary endpoints. However, when the primary endpoints involved different variables or time points in different efficacy studies, it may be useful to provide cross-study comparisons of important data elements that were obtained in all studies. If results over time are important, results of studies may be displayed in a figure that illustrates the change over time in each study.

Confidence intervals for treatment effects should be given to aid in the interpretation of point estimates. If differences are shown between placebo and test drugs in the change from baseline, the baseline values and the magnitude of effect in all treatment groups, including placebo and active controls (if used), should generally be presented in the table or in text accompanying a figure. If the objective of an active control trial was to show equivalence or non-inferiority, the difference or the ratio of outcomes between treatments should be given with the confidence interval. The results should be evaluated by using the predefined criteria for defining equivalence or non- inferiority and the rationale for the criteria and support for the determination that the study (studies) had assay sensitivity should be provided (see ICH E10).

Important differences in outcomes between studies with a similar design should be delineated and discussed. Cross- study comparisons of factors that may have contributed to differences in outcomes should be described.

If a meta-analysis of the clinical studies is performed, it should be clear whether this analysis is conducted according to a predefined protocol or is a post hoc exercise. Any differences in trial designs or populations, or in efficacy measurements between trials should be described to allow assessment of the relevance and validity of the results and conclusions (See ICH E9). A detailed description of the methodology and results of the meta-analysis should generally be submitted in a separate report (Clinical Study Reports).

3.3.3 Comparison of Results in Sub-populations

The results of individual studies or overview analyses of efficacy in specific populations should be summarized in this section. The purpose of these comparisons should be to show whether the claimed treatment effects are observed consistently across all relevant sub-populations, especially those where there are special reasons for concern. The comparisons may highlight apparent variations in efficacy that require further investigation and discussion. The limitations of such analyses, however, should be recognized (ICH E9), and it is important to note that their purpose is not to provide the basis for specific claims, nor to attempt to improve the evidence of efficacy in situations where the overall results are disappointing.

Given the limited sample sizes in individual studies, analyses across multiple studies should be performed to evaluate effects of major demographic factors (age, sex, and race) on efficacy. Factors of special interest may arise from general concerns (e.g., the elderly) or from specific issues that are related to the pharmacology of the drug or that have arisen during earlier drug development. Efficacy in the pediatric population should be routinely analyzed in applications for a proposed indication that occurs in children. Depending on the data set, if extensive,

detailed efficacy analyses are performed, they can be placed in Clinical Study Reports, with the results of those analyses reported here.

3.4 Analysis of Clinical Information Relevant to Dosing Recommendations

This section should provide an integrated summary and analysis of all data that pertain to the dose-response or blood level- response relationships of effectiveness (including dose-blood level relationships), and thus have contributed to dose selection and choice of dose interval. Relevant data from nonclinical studies may be referenced, and relevant data from pharmacokinetic studies, other clinical pharmacology studies, and controlled and uncontrolled clinical studies should be summarized to illustrate these dose-response or blood level-response relationships. For pharmacokinetic and pharmacodynamic studies from which data have been summarized in Item 2.2, it may be appropriate to draw upon those data in this summary while cross-referencing the summaries in Item 2.2, without repeating those summaries.

While the interpretation of how these data support specific dosing recommendations should be supplied in the Clinical Overview document, the individual study results and any cross-study analyses that will be used to support the dosing recommendations (including the recommended starting and maximal doses, the method of dose titration, and any other instructions regarding individualization of dosage) should be summarized here. Any identified deviations from relatively simple dose-response or blood-level response relationships due to non-linearity of pharmacokinetics, delayed effects, tolerance, enzyme induction, etc. should be described.

Any evidence of differences in dose-response relationships that result from a patient's age, sex, race, disease, or other factors should be described. Any evidence of different pharmacokinetic or pharmacodynamic responses should also be discussed, or discussions in Item 2 can be cross-referenced. The ways in which such differences were looked for, even if no differences were found, should be described (e.g., specific studies in subpopulations, analysis of efficacy results by subgroup, or blood level determinations of the test drug).

3.5 Persistence of Efficacy and/or Tolerance Effects

Available information on persistence of efficacy over time should be summarized. The number of patients for whom long-term efficacy data are available, and the length of exposure, should be provided. Any evidence of tolerance (loss of therapeutic effects over time) should be noted. Examination of any apparent relationships between dose changes over time and long-term efficacy may be useful.

The primary focus should be on controlled studies specifically designed to collect long- term efficacy data, and such studies should be clearly differentiated from other, less rigorous, studies such as open extension studies. This distinction also applies to specific studies designed for evaluation of tolerance and withdrawal effects. Data concerning withdrawal or rebound effects pertinent to product safety should be presented in the safety section (see Item 4).

In long-term efficacy trials, the effect of premature discontinuation of therapy or switching to other therapies upon the assessment of the results should be considered. These issues might also be important for short term trials and should be addressed when discussing the results of these trials, if appropriate.

4. SUMMARY OF CLINICAL SAFETY

This section should be a summary of data relevant to safety in the intended patient population, integrating the results of individual clinical study reports as well as other relevant reports, e.g., the integrated analyses of safety that are routinely submitted in some regions.

The display of safety-related data can be considered at three levels (ICH E3):

- The extent of exposure (dose, duration, number of patients, type of patients) should be examined to determine the degree to which safety can be assessed from the database.
- The more common adverse events and changes in laboratory tests should be identified and classified, and their occurrence should be summarized.
- Serious adverse events (defined in ICH E2A) and other significant adverse events (defined in ICH E3) should be identified and their occurrence should be summarized. These events should be examined for frequency over time, particularly for drugs that may be used chronically.

The safety profile of the drug, described on the basis of analysis of all clinical safety data, should be outlined in a detailed, clear, and objective manner, with use of tables and figures.

4.1 Exposure to the Drug

4.1.1 Overall Safety Evaluation Plan and Narratives of Safety Studies

The overall safety evaluation plan should be described briefly, including special considerations and observations concerning the nonclinical data, any relevant pharmacological class effects, and the sources of the safety data (controlled trials, open studies, etc). A tabular listing of all clinical studies that provided safety data, grouped appropriately, should generally be provided . In addition to studies that evaluated efficacy and safety, and uncontrolled studies that generate safety information, this section includes studies that consider special safety issues. Examples would include studies to compare particular adverse event rates for two therapies, to assess safety in particular demographic subsets, to evaluate withdrawal or rebound phenomena, or to evaluate particular adverse events (e.g., sedation, sexual function, effects on driving, absence of a class adverse effect). Studies in indications for which approval is not being sought in the current application and ongoing studies would also be included here if they contribute to the safety analysis.

Narrative descriptions of these studies should be provided here, except that narrative descriptions for studies that contributed both efficacy and safety data should be included in Item 3.2 and cross-referenced here. The narratives should provide enough detail to allow the reviewer to understand the exposure of study subjects to the test drug or control agent, and how safety data were collected (including the methods used and the extent of safety monitoring of the subjects enrolled in the individual studies). If some studies are not analyzed separately but are grouped for safety analysis, that should be noted, and a single narrative description can be provided.

4.1.2 Overall Extent of Exposure

A table and appropriate text should be generated to summarize the overall extent of drug exposure from all phases of the clinical study development program. The table should indicate the numbers of subjects exposed in studies of different types and at various doses, routes, and durations. If a large number of different doses and/ or durations of exposure were used, these

can be grouped in a manner appropriate for the drug. Thus, for any dose or range of doses, duration of exposure can be summarized by the number of subjects exposed for specific periods of time, such as 1 day or less, 2 days to 1 week, 1 week to 1 month, 1 month to 6 months, 6 months to 1 year, more than 1 year (ICH E3). In some applications it may be important to identify diagnostic subgroups and/or groups receiving specific concomitant therapies deemed particularly relevant to safety assessment in the intended use.

The dose levels used for each subject in this presentation could be the maximum dose received by that subject, the dose with longest exposure, and/or the mean daily dose, as appropriate. In some cases, cumulative dose may be pertinent. Dosage may be given as the actual daily dose or on a mg/kg or mg/ m2 basis, as appropriate. If available, drug concentration data (e.g., concentration at the time of an adverse event, maximum plasma concentration, area under curve) may be helpful in individual subjects for correlation with adverse events or changes in laboratory variables.

It is assumed that all subjects who were enrolled and received at least one dose of the treatment are included in the safety analysis; if that is not so, an explanation should be provided.

4.1.3 Demographic and Other Characteristics of Study Population

A summary table should provide the reader with an overview of the demographic characteristics of the population that was exposed to the therapeutic agent during its development. Choice of age ranges used should take into account considerations discussed in ICH E7 [Studies in Support of Special Populations: Geriatrics] and ICH E11 [Clinical Investigation of Medicinal Products in the Paediatric Population]. If the relative exposure of demographic groups in the controlled trials differed from overall exposure, it may be useful to provide separate tables.

In addition, one or more tables should show the relevant characteristics of the study population, and the numbers of subjects with special characteristics. Such characteristics could include:

- Severity of disease
- Hospitalization
- Impaired renal function
- Concomitant illnesses
- Concomitant use of particular medications
- Geographical location

If these characteristics are distributed differently in controlled trials versus the overall database, it will generally be useful to present tables on both groupings.

The text accompanying the table(s) should mention any imbalance(s) between the drug and placebo and/or comparator regarding any of the above demographic characteristics, particularly if they could lead to differences in safety outcomes.

If certain subjects were excluded from studies (concomitant illness, severity of illness, concomitant medications), this fact should be noted.

Separate demographic tables should be provided for every indication, although closely related indications can be considered together, if study subject characteristics are such that risks are believed to be the same.

4.2 Adverse Events

4.2.1 Analysis of Adverse Events

Data on the frequency of adverse events should be described in text and tables. Text should appear in the appropriate Item 4.2.1 and the tables that are not embedded in the text should be annexed.

All adverse events occurring or worsening after treatment has begun ("treatment emergent signs and symptoms," those adverse events not seen at baseline and those that worsened even if present at baseline) should be summarized in tables listing each event, the number of subjects in whom the event occurred and the frequency of occurrence in subjects treated with the drug under investigation, with comparator drugs, and with placebo. Such tables could also present results for each dose and could be modified to show, e.g., adverse event rates by severity, by time from onset of therapy, or by assessment of causality.

When most of the relevant safety data are derived from a small number of studies (e.g., one or two studies), or when very different study subject populations were enrolled in the studies that were performed, presentation of data by study will often be appropriate. When the relevant exposure data is not concentrated in a small number of studies, however, grouping the studies and pooling the results to improve precision of estimates and sensitivity to differences should generally be considered.

While often useful, pooling of safety data across studies should be approached with caution because in some cases interpretation can be difficult, and it can obscure real differences. In cases where differences are apparent, it is more appropriate to present the data by study. The following issues should be considered:

- it is most appropriate to combine data from studies that are of similar design, e.g., similar in dose, duration, methods of determining adverse events, and population.
- if the incidence for a particular adverse event differs substantially across the individual studies in a pool, the pooled estimate is less informative.
- any study with an unusual adverse event pattern should be presented separately.
- the appropriate extent of analysis depends on the seriousness of the adverse event and the strength of evidence of drug causation. Differences in rates of drug- related, serious events or events leading to discontinuation or dosage change deserve more investigation, whereas rates of other adverse events do not merit elaborate analysis.
- examination of which subjects experience extreme laboratory value abnormalities ("outliers") may be useful in identifying subgroups of individuals who are at particular risk for certain adverse events.

Groups of studies that could be used in pooled safety analyses include:

- all controlled studies or subsets of controlled studies, such as all placebo- controlled studies, studies with any positive control, studies with a particular positive control, or studies of particular indications (and thus carried out in different populations). These groupings are considered the best source of information about the more common adverse events and can distinguish drug-related events from spontaneous events. Rates in control and treatment groups should be compared.
- all studies, excluding short-term studies in healthy subjects. This grouping is most useful for evaluating rarer events.
- all studies using a particular dose route or regimen, or a particular concomitant therapy.
- studies in which adverse event reports are elicited by checklist or direct questioning, or

studies in which events are volunteered.
- pools of studies by region.

It is almost always useful to carry out the first two groupings; the others chosen would vary from drug to drug and should be influenced by inspection of individual study results. Whatever methods are used, it should be recognized that, as for results of single studies, any numerical rate is often only a rough approximation of reality.

When a decision is made to pool data from several studies, the rationale for selecting the method used for pooling should be described. It is common to combine the numerator events and the denominators for the selected studies. Other methods for pooling results across studies are available, e.g., weighting data from studies on the basis of study size or inversely to their variance.

If substantial differences are seen between clinical trials in the rates of adverse events, these differences should be noted and possible reasons should be discussed (e.g., relevant differences in study populations, in dose administration, or in methods of collecting adverse event data).

Adverse events should be described as shown in the individual study report (ICH E3). In combining data from many studies, it is important to use standardized terms to describe events and collect synonymous terms under a single preferred term. This can be done with international standard dictionary and terminology should be used and specified. Frequencies should be presented for preferred terms and for appropriately defined groupings. Examination of which adverse events led to change in therapy (discontinuation of drug use, change in dose, need for added therapy) can help in assessing the clinical importance of adverse events. These rates can be added to the adverse event rate tables, or can be presented in separate tables. Overall discontinuation rates by study may be useful but it is also important to specify the particular adverse events leading to discontinuation in a separate table. The preferred terms should be grouped by body system and arranged by decreasing frequency.

4.2.1.1 Common Adverse Events

Tabular displays of adverse event rates should be used to compare rates in treatment and control groups. For this analysis it may be helpful to combine the event severity categories and the causality categories, if they are used, leading to a simpler side-by-side comparison of treatment groups. It should be noted that while causality categories may be reported, if used, the presentation of the data should include total adverse events (whether deemed related or unrelated to treatment); evaluations of causality are inherently subjective and may exclude unexpected adverse events that are in fact treatment related. Additionally, comparisons of rates of adverse events between treatment and control groups in individual trials should be summarized here. It is often useful to tabulate rates in selected trials (see example table 4.4, in Appendix 4).

It is usually useful to examine more closely the more common adverse events that seem to be drug related (e.g., those that show that a dose response and/or a clear difference between drug and placebo rates) for relationship to relevant factors, including:
- dosage;
- mg/kg or mg/m2 dose;
- dose regimen;
- duration of treatment;
- total dose;

- demographic characteristics such as age, sex, race;
- concomitant medication use;
- other baseline features such as renal status;
- efficacy outcomes;
- drug concentration, where available.

It may also be useful to summarize the results of examination of time of onset and duration for these drug-related events.

Rigorous statistical evaluations of the possible relationship of specific adverse events to each of the above factors are often unnecessary. It may be apparent from initial display and inspection of the data that there is no evidence of a significant relationship to demographic or other baseline features. In that case, no further analysis of these particular factors is needed. Further, it is not necessary that all such analyses be presented in this report. When the safety analyses are too extensive to be presented in detail in this report, they may be presented in a separate report in Clinical Study Reports, and summarized here.

Under certain circumstances, life table or similar analyses may be more informative than reporting of crude adverse event rates.

4.2.1.2 Deaths

A table in Appendix 4 should list all deaths occurring while on study (including deaths that occurred shortly following treatment termination, e.g., within 30 days or as specified in the study protocol, as well as all other deaths that occurred later but may have resulted from a process that began during studies). Only deaths that are clearly disease-related per protocol definitions and not related to the investigational product, either in studies of conditions with high mortality such as advanced cancer or in studies where mortality from disease is a primary study endpoint, should be excepted from this listing (it is assumed, however, that these deaths would still be reported in the individual ICH E3 study reports). Even these deaths should be examined for any unexpected patterns between study arms, and further analysed if unexplained differences are observed. Deaths should be examined individually and analysed on the basis of rates in individual trials and appropriate pools of trials, considering both total mortality and cause- specific deaths. Potential relationships to the factors listed in Item 4.2.1.1 should also be considered. Although cause-specific mortality can be difficult to determine, some deaths are relatively easy to interpret. Thus, deaths due to causes expected in the patient population (heart attacks and sudden death in an angina population) are individually not considered to be informative, but even one death due to a QT interval prolongation- associated arrhythmia, aplastic anaemia, or liver injury may be informative. Special caution is appropriate before an unusual death is attributed to concomitant illness.

4.2.1.3 Other Serious Adverse Events

Summaries of all serious adverse events (other than death but including the serious adverse events temporally associated with or preceding the deaths) should be displayed. Serious adverse events that occurred after the drug use was discontinued should be included in this section. The display should include major laboratory abnormalities, abnormal vital signs, and abnormal physical observations that are considered serious adverse events using the ICH E2A definitions. Results of analyses or assessments of serious adverse events across studies should be presented. Serious events should be examined for frequency over time, particularly for drugs that may be used chronically. Potential relationships to the factors listed in Item 4.2.1.1 should

also be considered.

4.2.1.4 Other Significant Adverse Events

Marked haematologic and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to a substantial intervention (premature discontinuation of study drug, dose reduction, or substantial additional concomitant therapy), other than those reported as serious adverse events, should be displayed.

Events that led to premature discontinuation of study drug represent an important safety concern and deserve particular attention in the analysis of drug safety for two reasons. First, even for expected events (based on pharmacologic activity), the need to discontinue (or otherwise alter) treatment reflects the severity and perceived importance of the event to patient and physician. Second, discontinuation may represent a drug- related event not yet recognised as drug related. Adverse events leading to treatment discontinuation should be considered possibly drug-related even if this was not recognised initially and even if the event was thought to represent intercurrent illness. Reasons for premature treatment discontinuations should be discussed and rates of discontinuations should be compared across studies and compared with those for placebo and/or active control treatment. In addition, the study data should be examined for any potential relationships to the factors listed in Item 4.2.1.1.

4.2.1.5 Analysis of Adverse Events by Organ System or Syndrome

Assessment of the causality of, and risk factors for, deaths, other serious events, and other significant events is often complicated by the fact that they are uncommon. As a result, consideration of related events as a group, including less important events of potentially related pathophysiology, may be of critical value in understanding the safety profile. For example, the relationship to treatment of an isolated sudden death may become much clearer when considered in the context of cases of syncope, palpitations, and asymptomatic arrhythmias.

It is thus generally useful to summarize adverse events by organ system so that they may be considered in the context of potentially related events including laboratory abnormalities. Such presentations of adverse events by organ system should be placed in Item 4.2.1.5, labelled as 4.2.1.5.1, 4.2.1.5.2, etc., and titled by the organ system under consideration. The list of organ systems to be addressed and the approach to grouping certain events should be selected as appropriate to best present the adverse event data for the medicinal product. If some adverse events tend to occur in syndromes (e.g., influenza- like syndrome, cytokine release syndrome), the sponsor may choose to create some Item 4.2.1.5 for syndromes rather than organ systems.

The same data and summarizations should generally not be repeated in more than one subsection of Item 4.2.1. Instead, a summary presentation may be placed in one subsection and cross-referenced as needed in the other.

4.2.2 Narratives

The locations in the application of individual narratives of patient deaths, other serious adverse events, and other significant adverse events deemed to be of special interest because of clinical importance (as described in ICH E3 individual study reports) should be referenced here for the convenience of the reviewer. The narratives themselves should be a part of the individual study reports, if there is such a report. In cases where there is no individual study report (e.g., if many open studies are pooled as part of a safety analysis and are not individually described),

narratives can be placed in Clinical Study Reports, Item 5.3. Narratives should not be included here, unless an abbreviated narrative of particular events is considered critical to the summary assessment of the drug.

4.3 Clinical Laboratory Evaluations

This section should describe changes in patterns of laboratory tests with drug use. Marked laboratory abnormalities and those that led to a substantial intervention should be reported in Item 4.2.1.3 or 4.2.1.4. If these data are also presented in this section, this duplicate reporting should be made clear for the reviewer. The appropriate evaluations of laboratory values will in part be determined by the results seen, but, in general, the analyses described below should be provided. For each analysis, comparison of the treatment and control groups should be carried out, as appropriate and as compatible with study sizes. In addition, normal laboratory ranges should be given for each analysis (ICH E3). Where possible, laboratory values should be provided in standard international units.

A brief overview of the major changes in laboratory values across the clinical studies should be provided. Laboratory data should include haematology, clinical chemistry, urinalysis and other data as appropriate. Each parameter at each time over the course of the study (e.g., at each visit) should be described at the following three levels:

- the central tendency, i.e., the group mean and median values,
- the range of values, and the number of subjects with abnormal values or with abnormal values of a certain size (e.g. twice the upper limit of normal, 5 times the upper limit; choices should be explained). When data are pooled from centers with differences in normal laboratory ranges, the methodology used in pooling should be described. The analysis of individual subject changes by treatment group can be shown with a variety of approaches (e.g., shift tables, see ICH E3 for examples).
- individual clinically important abnormalities, including those leading to discontinuations. The significance of the laboratory changes and the likely relation to the treatment should be assessed (e.g., by analysis of such features as relationship to dose, relation to drug concentration, disappearance on continued therapy, positive dechallenge, positive rechallenge, and the nature of concomitant therapy). Potential relationships to other factors listed in Item

4.2.1.1 should also be considered.

4.4 Vital Signs, Physical findings, and Other Observations Related to Safety

The manner of presenting cross-study observations and comparisons of vital signs (e.g., heart rate, blood pressure, temperature, respiratory rate), weight and other data (e.g., electrocardiograms, X-rays) related to safety should be similar to that for laboratory variables. If there is evidence of a drug effect, any dose-response or drug concentration- response relationship or relationship to individual variables (e.g., disease, demographics, concomitant therapy) should be identified and the clinical relevance of the observation described. Particular attention should be given to changes not evaluated as efficacy variables and to those considered to be adverse events. Particular attention should be given to studies that were designed to evaluate specific safety issues, e.g., studies of QT interval prolongation.

4.5 Safety in Special Groups and Situations

4.5.1 Patient Groups

This section should summarize safety data pertinent to individualizing therapy or patient management on the basis of demographic, age, sex, height, weight, lean body mass, genetic polymorphism, body composition, other illness and organ dysfunction. Safety in the pediatric population should be routinely analyzed in applications for a proposed indication that occurs in children. Analysis of the impact on safety outcomes should have been presented in other sections but should be summarized here, together with pertinent PK or other information, e.g., in patients with renal or hepatic disease, the medical environment, use of other drugs (see 4.5.2, Drug Interactions), use of tobacco, use of alcohol, and food habits. For example, if a potential interaction with alcohol is suggested by the metabolic profile, by the results of studies, by post-marketing experience, or by information on similar drugs, information should be provided here. If a sufficiently large number of subjects with a given co-morbid condition such as hypertension, heart disease, or diabetes, was enrolled, analyses should be carried out to assess whether the co- morbid condition affected the safety of the drug under study. Cross reference should be made to the tables or description of adverse events when analyses of such sub-groups has been carried out.

4.5.2 Drug Interactions

Studies on potential drug-drug or drug-food interactions should be summarized in the Summary of Clinical Pharmacology Studies section of the ACTD. The potential impact on safety of such interactions should be summarized here, based on PK, PD, or clinical observations. Any observed changes in the adverse event profile, changes in blood levels thought to be associated with risk, or changes in drug effects associated with other therapy should be presented here.

4.5.3 Use in Pregnancy and Lactation

Any information on safety of use during pregnancy or breast- feeding that becomes available during clinical development or from other sources should be summarized here.

4.5.4 Overdose

All available clinical information relevant to overdose, including signs/symptoms, laboratory findings, and therapeutic measures/treatments and antidotes (if available) should be summarized and discussed. Information on the efficacy of specific antidotes and dialysis should be provided if available.

4.5.5 Drug Abuse

Any relevant studies/information regarding the investigation of the dependence potential of a new therapeutic agent in animals and in humans should be summarized and cross- referenced to the nonclinical summary. Particularly susceptible patient populations should be identified.

4.5.6 Withdrawal and Rebound

Any information or study results pertinent to rebound effects should be summarized. Events that occur, or increase in severity, after discontinuation of double-blind or active study medication should be examined to see if they are the result of withdrawal of the study

medication. Particular emphasis should be given to studies designed to evaluate withdrawal and/or rebound.

Data concerning tolerance should be summarized under Item 3.5 in the Summary of Clinical Efficacy.

4.5.7 Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

Safety data related to any impairment in the senses, co- ordination, or other factor that would result in diminished ability to drive a vehicle or operate machinery or that would impair mental ability should be summarized. This includes relevant adverse effects reported in safety monitoring (e.g., drowsiness) and specific studies concerning effects on ability to drive or operate machinery or impairment of mental ability.

4.6 Post-marketing Data

If the drug has already been marketed, all relevant post-marketing data available to the applicant (published and unpublished, including periodic safety update reports if available) should be summarized. The periodic safety update reports can be included in Clinical Study Reports. Details of the number of subjects estimated to have been exposed should be provided and categorized, as appropriate, by indication, dosage, route, treatment duration, and geographic location. The methodology used to estimate the number of subjects exposed should be described. If estimates of the demographic details are available from any source, these should be provided.

A tabulation of serious events reported after the drug is marketed should be provided, including any potentially serious drug interactions.

Any post-marketing findings in subgroups should be described.

5. SYNOPSES OF INDIVIDUAL STUDIES

The ICH E3 guideline (Structure and Content of Clinical Study Reports) suggests inclusion of a study synopsis with each clinical study report, and provides one example of a format for such synopses.

This section should include the table entitled Listing of Clinical Studies, described in guidance for Clinical Study Reports, followed by all individual study synopses organised in the same sequence as the study reports in Clinical Study Reports.

It is expected that one synopsis will be prepared per study for use in all regions, and that the same synopsis will be included in this section and as part of the clinical study report.

The length of a synopsis will usually be up to 3 pages, but a synopsis for a more complex and important study may be longer, e.g. 10 pages. Within the individual synopsis, tables and figures should be used as appropriate to aid clarity.

SECTION D: TABULAR LISTING Of ALL CLINICAL STUDIES

A tabular listing of all clinical studies and related information should be provided. For each study, this tabular listing should generally include the type of information identified in Table 1 of this guideline. Other information can be included in this table if the applicant considers it useful. The sequence in which the studies are listed should follow the sequence described in E: Clinical Study Reports.

Table 1. Listing of Clinical Studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report

Section E: Clinical Study Reports Preamble

For ASEAN member countries, the Study Reports of this part may not be required for NCE, Biotechnological Products and other Major Variation Products if the Original Products are already registered and approved for market authorization in Reference Countries. Therefore, the Department of Drug and Food may request specific Study Reports when necessary. The ICH E3 provides guidance on the organization of clinical study reports, other clinical data, and references within the ASEAN Common Technical Dossier (ACTD) for registration of a pharmaceutical product for human use. In this case, the applicant will submit Section A, B, C. D and F.

Guideline on Organization of Clinical Study Reports and Related Information

This guideline recommends a specific organization for the placement of clinical study reports and related information to simplify preparation and review of dossiers and to ensure completeness. The placement of a report should be determined by the primary objective of the study. Each study report should appear in only one section. Where there are multiple objectives, the study should be cross-referenced in the various sections.

An explanation such as “not applicable” or “no study conducted” should be provided when no report or information is available for a section or subsection.

A. Table of Contents For Study Reports

A Table of Contents for the study reports should be provided.

B. Tabular Listing of All Clinical Studies

A tabular listing of all clinical studies and related information should be provided. For each study, this tabular listing should generally include the type of information identified in Table 1 of this guideline. Other information can be included in this table if the applicant considers it useful. The sequence in which the studies are listed should follow the sequence described in Section C below. Use of a different sequence should be noted and explained in an introduction to the tabular listing.

C. Clinical Study Reports

1. Reports of Biopharmaceutics Studies

BA studies evaluate the rate and extent of release of the active substance from the medicinal product. Comparative BA or BE studies may use PK, PD, clinical, or in vitro dissolution endpoints, and may be either single dose or multiple dose. When the primary purpose of a study is to assess the PK of a drug, but also includes BA information, the study report should be submitted in Item 3.1, and referenced in Items 1.1 and/or 1.2.

1.1 Bioavailability (BA) Study Reports

BA studies in this section should include 1) studies comparing the release and systemic

availability of a drug substance from a solid oral dosage form to the systemic availability of the drug substance given intravenously or as an oral liquid dosage form 2) dosage form proportionality studies, and 3) food-effect studies.

1.2 Comparative BA and Bioequivalence (BE) Study Reports

Studies in this section compare the rate and extent of release of the drug substance from similar drug products (e.g., tablet to tablet, tablet to capsule). Comparative BA or BE studies may include comparisons between 1) the drug product used in clinical studies supporting effectiveness and the to-be-marketed drug product, 2) the drug product used in clinical studies supporting effectiveness and the drug product used in stability batches, and 3) similar drug products from different manufacturers.

1.3 In Vitro – In Vivo Correlation Study Reports

In vitro dissolution studies that provide BA information, including studies used in seeking to correlate in vitro data with in vivo correlations, should be placed in Item 1.3.

Reports of in vitro dissolution tests used for batch quality control and/ or batch release should be placed in the Quality section of the ACTD.

1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

Bioanalytical and/or analytical methods for biopharmaceutic studies or in vitro dissolution studies should ordinarily be provided in individual study reports. Where a method is used in multiple studies, the method and its validation should be included once in Item 1.4 and referenced in the appropriate individual study reports.

2. Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials

Human biomaterials is a term used to refer to proteins, cells, tissues and related materials derived from human sources that are used in vitro or ex vivo to assess PK properties of drug substances. Examples include cultured human colonic cells that are used to assess permeability through biological membranes and transport processes, and human albumin that is used to assess plasma protein binding. Of particular importance is the use of human biomaterials such as hepatocytes and/or hepatic microsomes to study metabolic pathways and to assess drug-drug interactions with these pathways.

Studies using biomaterials to address other properties (e.g., sterility or pharmacodynamics) should not be placed in the Clinical Study Reports Section, but in the Nonclinical Study Section (Part III).

2.1 Plasma Protein binding Study Reports

Ex vivo protein binding study reports should be provided here.

Protein binding data from PK blood and/or plasma studies should be provided in Item 3.

2.2 Reports of Hepatic Metabolism and Drug Interaction Studies

Reports of hepatic metabolism and metabolic drug interaction studies with hepatic tissue should be placed here.

2.3 Studies Using Other Human biomaterials

Reports of studies with other biomaterials should be placed in this section.

3. Reports of Human Pharmacokinetic (PK) Studies

Assessment of the PK of a drug in healthy subjects and/or patients is considered critical to designing dosing strategies and titration steps, to anticipating the effects of concomitant drug use, and to interpreting observed pharmacodynamic differences. These assessments should provide a description of the body's handling of a drug over time, focusing on maximum plasma concentrations (peak exposure), area-under-curve (total exposure), clearance, and accumulation of the parent drug and its metabolite(s), in particular those that have pharmacological activity. The PK studies whose reports should be included in Item 3.1 and 3.2 are generally designed to (1) measure plasma drug and metabolite concentrations over time, (2) measure drug and metabolite concentrations in urine or feces when useful or necessary, and/or (3) measure drug and metabolite binding to protein or red blood cells.

On occasion, PK studies may include measurement of drug distribution into other body tissues, body organs, or fluids (e.g., synovial fluid or cerebrospinal fluid), and the results of these tissue distribution studies should be included in Item 3.1 to 3.2, as appropriate. These studies should characterise the drug's PK and provide information about the absorption, distribution, metabolism, and excretion of a drug and any active metabolites in healthy subjects and/or patients. Studies of mass balance and changes in PK related to dose (e.g., determination of dose proportionality) or time (e.g., due to enzyme induction or formation of antibodies) are of particular interest and should be included in Item 3.1 and/or 3.2. Apart from describing mean PK in normal and patient volunteers, PK studies should also describe the range of individual variability.

3.1 Healthy Subject PK and Initial Tolerability Study Reports

Reports of PK and initial tolerability studies in healthy subjects should be placed in this section.

3.2 Patient PK and Initial Tolerability Study Reports

Reports of PK and initial tolerability studies in patients should be placed in this section.

3.3 Population PK Study Reports

Reports of population PK studies based on sparse samples obtained in clinical trials including efficacy and safety trials, should be placed in this section.

4. Reports of Human Pharmacodynamic (PD) Studies

Reports of studies with a primary objective of determining the PD effects of a drug product in humans should be placed in this section. Reports of studies whose primary objective is to establish efficacy or to accumulate safety data, however, should be placed in Item 5.

This section should include reports of 1) studies of pharmacologic properties known or thought to be related to the desired clinical effects (biomarkers), 2) short-term studies of the main clinical effect, and 3) PD studies of other properties not related to the desired clinical effect. Because a quantitative relationship of these pharmacological effects to dose and/or plasma drug and metabolite concentrations is usually of interest, PD information is frequently collected in dose response studies or together with drug concentration information in PK studies (concentration- response or PK/PD studies). Relationships between PK and PD effects that are not obtained in well-controlled studies are often evaluated using an appropriate model and used as a basis for designing further dose-response studies or, in some cases, for interpreting effects of concentration differences in population subsets.

Dose-finding, PD and/or PK-PD studies can be conducted in healthy subjects and/or patients, and can also be incorporated into the studies that evaluate safety and efficacy in a clinical indication. Reports of dose-finding, PD and/or PK/PD studies conducted in healthy subjects should be placed in Item 4.1, and the reports for those studies conducted in patients should be placed in Item 4.2.

In some cases, the short-term PD, dose-finding, and/or PK-PD information found in pharmacodynamic studies conducted in patients will provide data that contribute to assessment of efficacy, either because they show an effect on an acceptable surrogate marker (e.g., blood pressure) or on a clinical benefit endpoint (e.g., pain relief). Similarly, a PD study may contain important clinical safety information. When these studies are part of the efficacy or safety demonstration, they are considered clinical efficacy and safety studies that should be included in Item 5, not in Item 4.

4.1 Healthy Subject PD and PK/PD Study Reports

PD and/or PK/PD studies having non-therapeutic objectives in healthy subjects should be placed in this section

4.2 Patient PD and PK/PD Study Reports

PD and/or PK/PD studies in patients should be submitted in this section.

5. Reports of Efficacy and Safety Studies

This section should include reports of all clinical studies of efficacy and/or safety carried out with the drug, conducted by the sponsor, or otherwise available, including all completed and all ongoing studies of the drug in proposed and non-proposed indications. The study reports should provide the level of detail appropriate to the study and its role in the application. ICH E3 describes the contents of a full report for a study contributing evidence pertinent to both safety and efficacy. Abbreviated reports can be provided for some studies (see ICH E3 and individual guidance by region).

Within Item 5, studies should be organized by design (controlled, uncontrolled) and, within controlled studies, by type of control. Within each section, studies should be categorized further, ordered by whether the study report is complete or abbreviated (ICH E3), with completely reported studies presented first. Published reports with limited or no further data available to the sponsor should be placed last in this section.

In cases where the application includes multiple therapeutic indications, the reports should be

organized in a separate Item 5 for each indication. In such cases, if a clinical efficacy study is relevant to only one of the indications included in the application, it should be included in the appropriate Item 5; if a clinical efficacy study is relevant to multiple indications, the study report should be included in the most appropriate Item 5 and referenced as necessary in other Items 5, e.g., Item 5A, Item 5B.

5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

The controlled clinical study reports should be sequenced by type of control:

- Placebo control (could include other control groups, such as an active comparator or other doses)
- No-treatment control
- Dose-response (without placebo)
- Active control (without placebo)
- External (Historical) control, regardless of the control treatment

Within each control type, where relevant to assessment of drug effect, studies should be organized by treatment duration. Studies of indications other than the one proposed in the application, but that provide support for efficacy in the proposed use, should be included in Item 5.1.

Where a pharmacodynamic study contributes to evidence of efficacy, it should be included in Item 5.1. The sequence in which studies were conducted is not considered pertinent to their presentation. Thus, placebo-controlled trials, whether early or late, should be placed in Item 5.1. Controlled safety studies, including studies in conditions that are not the subject of the application, should also be reported in Item 5.1.

5.2 Study Reports of Uncontrolled Clinical Studies

Study reports of uncontrolled clinical studies (e.g., reports of open label safety studies) should be included. This includes studies in conditions that are not the subject of the marketing application.

5.3 Reports of Analyses of Data from More than One Study

Many clinical issues in an application can be addressed by an analysis considering data from more than one study. The results of such an analysis should generally be summarized in the clinical summary documents, but a detailed description and presentation of the results of such analyses are considered critical to their interpretation. Where the details of the analysis are too extensive to be reported in a summary document, they should be presented in a separate report. Such reports should be placed in Item 5.3. Examples of reports that would be found in this section include: a report of a formal meta-analysis or extensive exploratory analysis of efficacy to determine an overall estimate of effect size in all patients and/or in specific subpopulations, and a report of an integrated analysis of safety that assesses such factors as the adequacy of the safety database, estimates of event rates, and safety with respect to variables such as dose, demographics, and concomitant medications.

5.4 Other Clinical Study Reports

This section can include:

- − Reports of interim analyses of studies pertinent to the claimed indications
- − Reports of controlled safety studies not reported elsewhere
- − Reports of controlled or uncontrolled studies not related to the claimed indication
- − Published reports of clinical experiences with the medicinal product that are not included in Item 5.1. However, when literature is important to the demonstration or substantiation of efficacy, it should be included in Item 5.1
- − Reports of ongoing studies

6. Reports of Post-Marketing Experience

For products that are currently marketed, reports that summarize marketing experience (including all significant safety observations) should be included in Item 6.

7. Case Report forms and Individual Patient Listings

Case report forms and individual patient data listings that are described as appendices 16.3 and 16.4 in the ICH clinical study report guideline, should be placed in this section when submitted, in the same order as the clinical study reports and indexed by study.

Section F: List of Key Literature References

List of referenced documents, including important published articles, official meeting minutes, or other regulatory guidance or advice should be provided here. This includes all references cited in the Clinical Overview, and important references cited in the Clinical Summary or in the individual technical reports that were provided in Clinical Study Reports. Finally, copies of referenced documents should be available upon request.

CTD CLINICAL CHECK LIST FOR PRODUCT CLASSIFICATION

(Adapted from ASEAN Common Technical Dossier for Pharmaceutical Registration)

For appendices refer to ATCD checklist

Part IV: Clinical Document	NCE	BIOTECH		MaV		MiV	GP
			RT	ST/P	IND		
Section A. Table of Contents	✓	✓	✓	✓	✓	-	-
Section B. Clinical Overview 1. Product Development Rationale 2. Overview of Biopharmaceutics 3. Overview of Clinical Pharmacology 4. Overview of Efficacy 5. Overview of Safety 6. Benefits and Risks Conclusions	✓	✓	✓	✓	✓	-	-
Section C. Clinical Summary **1. Summary of biopharmaceutic Studies and Associated Analytical Method** 1.1 Background and Overview 1.2 Summary of Results of Individual Studies 1.3 Comparison and Analyses of Results Across Studies Appendix 1 **2. Summary of Clinical Pharmacology Studies** 2.1 Background and Overview 2.2 Summary of Results of Individual Studies 2.3 Comparison and Analyses of Results Across Studies 2.4 Special Studies Appendix 2	✓	✓	✓	✓	✓	-	-

Part IV: Clinical Document	NCE	BIOTECH	RT	MaV ST/P	IND	MiV	GP
3. Summary of Clinical Efficacy 3.1 Background and Overview of Clinical Efficacy 3.2 Summary of Results of Individual Studies 3.3 Comparison and Analyses of Results Across Studies 3.4 Analysis of Clinical Information Relevant to Dosing Recommendations 3.5 Persistence of Efficacy and/or Tolerance Effects Appendix 3 **4. Summary of Clinical Safety** 4.1 Exposure to the Drug 4.2 Adverse Events 4.3 Clinical Laboratory Evaluations 4.4 Vital Signs, Physical Findings, and Other Observation Related to safety 4.5 Safety in Special Groups and Situations 4.6 Post-marketing Data Appendix 4 **5.Synopses of Individual Studies**							
Section D. Tabular Listing of All Clinical Studies	✓	✓	✓	✓	✓	-	-
Section E. Clinical Study Reports (if applicable) **1. Reports of biopharmaceutic Studies** 1.1 BA Study Reports 1.2 Comparative BA or BE Study Reports 1.3 In vitro-In vivo Correlation Study Reports 1.4 Reports of Bioanalytical and Analytical Methods for Human Studies	✓	✓	✓	✓	✓	-	-

Part IV: Clinical Document	NCE	BIOTECH	RT	MaV ST/P	IND	MiV	GP
2. Reports of Studies Pertinent to Pharmacokinetics using Human biomaterials 2.1 Plasma Protein Binding Study Reports 2.2 Reports of Hepatic Metabolism and Drug Interaction Studies 2.3 Reports of Studies Using Other Human Biomaterials **3. Reports of Human Pharmacokinetic (PK) Studies** 3.1 Heatthy Subiect PK and Initial Tolerability Study Reports 3.2 Patient PK and Initial Tolerability Study Reports 3.3 Population PK Study Reports **4. Reports of Human Pharmacodynamic (PD) Studies** 4.1 Healthy Subject PD and PK/PD Study Reports 4.2 Patient PD and PK/PD Study Reports **5. Reports of Efficacy and Safety Studies** 5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication 5.2 Study Reports of Uncontrolled Clinical Studies 5.3 Reports of Analyses of Data from More Than One Study, Including Any Formal Integrated Analyses, Meta-analyses, and Bridging Analyses 5.4 Other Clinical Study Reports **6. Reports of Post-Marketing Experience** **7. Case Report forms and Individual Patient Listing**							
Section F. List of Key Literature References							

Chapter I Variation Guideline for Therapeutic Products

1. Introduction

Throughout the life of a pharmaceutical product, the marketing authorization holder is responsible for the product that is placed in the market and is also required to take into account technical and scientific progress, and to make any amendments that may be required to enable the pharmaceutical products to be manufactured and checked by means of generally accepted scientific methods. Such amendments have to be approved by DDF.

This guidance document is intended to provide supportive information on the requirements for submission of a variation application to implement a change to a pharmaceutical product. Variation applications are categorized into major variation, minor variation (prior approval) and minor variation (notification). Updating of this guideline will be done on a periodic basis as required.

2. Scope of this Guideline

This Variation Guideline concerns the variation applications submitted by the marketing authorization holder for pharmaceutical products for human use only and not including biologics.

3. Definition

3.1 Major variation (MaV)

Variation to a registered pharmaceutical finished product that may affect significantly and/or directly the aspects of quality, safety and efficacy and it does not fall within the definition of minor variation and new registration.

3.2 Minor Variation (MiV-N & MiV-PA)

Variation to a registered pharmaceutical finished product in terms of administrative data and/or changes with minimal/no significant impact on the aspects of efficacy, quality, and safety.

4. Procedure and Timeline

Variation application is submitted along with a declaration letter undersigned by the Head of Regulatory Officer that declares there is no other change except for the proposed variation

4.1 Minor Variation – Notification

Type of variation	**Minor variation (Notification) MiV-N**
Procedure	Notification "Do & Tell" If the notification fulfils the requirements (conditions and supporting documents) as per described under MiV-N, DDF will acknowledge receipt of a valid notification.
Timeline for DDF to acknowledge the variation notification	Within a duration subject to country specific proposal, following receipt of a valid notification.

4.2 Minor Variation –Prior Approval and Major Variation

Type of variation	**Minor variation (Prior approval) MiV-PA**	**Major variation MaV**
Procedure	Prior approval If the application fulfils the requirements (conditions and supporting documents) as per described under MiV-PA, DDF will issue an approval for the proposed change.	Prior approval If the application fulfils the requirements (conditions and supporting documents) as per described under MaV, DDF will issue an approval for the proposed change.
Timeline for DDF to evaluate the variation application	Within a duration subject to country specific proposal following receipt of a valid application.	Within a duration subject to country specific proposal following receipt of a valid application.
Implementation of the variation	Within a duration subject to country specific proposal after the marketing authorization holder has been informed of the approved variations.	

Note:

1. The 'timeline' and 'implementation of the variation' is subject to country specific proposals and be made publicly available.

2. DDF reserves the right to re-categorize the application type, where deemed appropriate. Subject to country specific procedure, re-categorization may require the marketing authorization holder to withdraw the original application and resubmit a new application according to the correct category.

5. Changes Leading to A New Product Registration

Changes requiring a new product registration may vary from country to country. Certain variations described in this guideline may require a new product registration in certain countries. Applicants are advised to check with individual country on the applicability of this variation guideline

6. Others

Lead compendium refers to British Pharmacopeia (BP), United States Pharmacopeia (USP) and European Pharmacopeia (EP).

Any variations not yet listed in this guideline should be justified and decided by DDF. Appropriate reference can be made to:

1. EMA Classification Guidance on Minor Variations of Type IA, Minor Variations of Type IB And Major Variations of Type II.

2. SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, And In Vivo Bioequivalence Documentation.

3. SUPAC-MR: Modified Release Solid, Oral Dosage Forms, Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation.

4. WHO Guidance on Variations to A Prequalified Product Dossier.

DDF reserves the right to request for additional information, when deemed necessary.

Abbreviations:

- C = Conditions to be fulfilled
- D = Documents to be submitted
- MaV = Major Variation
- MiV-N = Minor Variation (Notification)
- MiV-PA = Minor Variation (Prior Approval)

7. Major Variation

Major Variation (MaV)	
MaV-1	**Change and/or additional indication/dosing regimen/patient population/inclusion of clinical information extending the usage of the product**
C	1. Product labeling refers to Package Insert (PI), Patient Information Leaflet (PIL), unit carton label, inner label and/or blister strips. 2. As a subsequent change due to revision of Summary of Product Characteristics (SmPC) or equivalent document (USPI).
D	1. Approved product labeling. 2. Proposed product labeling, a clean and annotated version highlighting the changes made. 3. Approved PI/SmPC/PIL from an approved reference regulatory agency or the country of origin containing the proposed changes (where applicable). 4. Justifications for the changes proposed. 5. Approval letters from reference countries or country of origin which have approved the proposed indication or dosing regimen (where applicable). 6. Clinical expert reports and/or clinical trial reports (where applicable). 7. Clinical documents as per ASEAN Common Technical Dossier (ACTD) part IV (where applicable).
MaV-2	**Change of content of product labeling**
C	1. Product labeling refers to Package Insert (PI), Patient Information Leaflet (PIL), unit carton label, inner label and/or blister strips. The change is not a minor variation and not within the scope of MaV-1. As a subsequent change due to revision of Summary of Product Characteristics (SmPC) or equivalent document (USPI).
D	1. Approved product labeling. 2. Proposed product labeling, a clean and annotated version highlighting the changes made. 3. Approved PI/SmPC/PIL from an approved reference regulatory agency or the country of origin containing the proposed changes (where applicable). 4. Justifications for the changes proposed and supporting clinical documents when applicable.

MaV-3	**Addition or replacement of alternative manufacturer/site of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]**
C	1. Specifications of drug substances remain unchanged. 2. For Change and/or addition of alternative manufacturer/site of drug substance where European Pharmacopoeial Certificate of Suitability (CEP) is available, please refer to MiV-PA4.
D	1. Complete ACTD section S1-S7, or both the open and closed part of the Drug Master File (closed part may be provided directly by manufacturer) with the Letter of Access or equivalent audit document/certification from reference country which is deemed appropriate by DDF. 2. Comparative tabulated format of the approved and proposed drug substance manufacture information (where applicable). 3. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) for at least two pilot batches of the drug substance from the approved and proposed manufacturing sites. 4. A letter of commitment from marketing authorization holder to conduct long term and accelerated stability studies for the drug product manufactured with the drug substance from the proposed manufacturing site, and report if any results fall outside shelf-life specifications (with proposed action) or when requested.

MaV-4	**Addition or replacement of the manufacturing site of the drug product**
C	1. Not applicable to changes relating to manufacturer responsible for batch release or a site where only batch release takes place. 2. For addition or replacement of the company or party responsible for batch release, please refer to MiV-PA3. 3. If there are changes to the manufacturing process, MaV-9 is also applicable.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Proof that the proposed site is appropriately authorized for the pharmaceutical form concerned such as a valid Good Manufacturing Practice (GMP) certificate and/or a Certificate of Pharmaceutical Product (CPP) which covers GMP certification. 3. Batch numbering system (where applicable). 4. In case of a contract manufacturer, letter of appointment and letter of acceptance for the proposed site to manufacture the product and stating the types of activity to be performed (where applicable). 5. Specification of drug substance. 6. Product formula and/or batch manufacturing formula. 7. Comparative dissolution profile data of at least one pilot/production batch of the drug product manufactured in the approved and proposed manufacturing site for oral solid dosage forms as per compendium and validated dissolution test method. 8. Validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration at the proposed site should be provided upon submission. 9. Holding time studies testing of bulk pack during storage and transportation between the bulk production site and primary packager (where applicable). 10. Release and shelf-life specifications of drug product. 11. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product of at least two production batches (or one production batch and two pilot batch) from the proposed site and last three batches from the approved site; batch analysis data on the next two full production batches should be available upon request or reported if outside specifications (with proposed action). 12. Stability data as per ASEAN Guideline on Stability Study of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 13. Justification for not submitting a new bioequivalence study according to ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies (where applicable).

MaV-5	**Addition or replacement of alternative site for primary packaging (direct contact with drug product) for sterile product**
C	1. No other changes except for the addition or replacement of alternative site for primary packaging (direct contact with drug product). 2. For addition or replacement of alternative site for primary packaging (direct contact with drug product) for non-sterile product, please refer to MiV-PA36.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Proof that the proposed site is appropriately authorized for the packaging activity of the pharmaceutical form concerned–such as a valid GMP Certificate and/or a CPP which covers GMP certification. 3. In case of a contract primary packager, letter of appointment and letter of acceptance for the proposed site to package the product and stating the types of activity to be performed by the packager (where applicable). 4. Validation scheme and/or report on primary packaging processes as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration at the proposed site should be provided upon submission. 5. Holding time studies testing of bulk pack during storage and transportation between the bulk production site to primary packager (where applicable). 6. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action).

MaV-6	**Change of the specification of drug substance and/or drug product [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]** **a) Specification limits are widened** **b) Deletion of test parameter and limits**
C	1. Test procedures remain unchanged, or changes in the test procedure are minor. 2. Not applicable to compendial drug substances/drug products. 3. The change should not be the result of unexpected events arising during manufacture or because of stability concerns; unless otherwise justified. 4. For change of specification of drug substance where a CEP is available, please refer to MiV-PA12.
D	**a) Specification limits are widened** 1. Revised specification of drug substance / drug product. 2. Comparative tabulated format of the approved and proposed specification of drug substance/drug product with changes highlighted. 3. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of the drug substance/drug product for all tests in the proposed specification for two pilot or production scale batches. 4. Justification for change substantiated with scientific data to be provided. 5. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). **b) Deletion of test parameter and limits** 1. All of the above documents except D5.
MaV-7	**Change of batch size of sterile drug product**
C	1. The change does not affect consistency of production. 2. The product formulation remains unchanged. 3. Release and shelf-life specifications of drug product remain unchanged. 4. Process validation scheme and/or report is available or validation of the manufacturing process has been successfully carried out according to protocol with at least three batches appropriate to the proposed batch size in accordance with the ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration.
D	1. Comparative tabulated format of approved and proposed batch manufacturing formula. 2. Validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration of the proposed batch size should be provided upon submission. 3. Release and shelf-life specifications of the drug product. 4. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product of at least two production batches manufactured according to approved and proposed batch sizes. 5. Stability data as per ASEAN Guideline on Stability Study of Drug Product and report if any results fall outside shelf-life specifications (with proposed action).

MaV-8	**Change of batch size of non-sterile drug product**
C	1. The change does not affect consistency of production. 2. The product formulation remains unchanged. 3. Release and shelf-life specifications of drug product remain unchanged. 4. Process validation scheme and/or report is available or validation of the manufacturing process has been successfully carried out according to protocol with at least three batches appropriate to the proposed batch size in accordance with the ASEAN Guideline on Submission of Manufacturing Process Validation Data For Drug Registration. 5. This is applicable to change of batch size more than 10-fold compared to the approved batch size. For change of batch size up to 10-fold compared to the approved batch size, please refer MiV-PA13.
D	1. Comparative dissolution profile data of at least one pilot/production batch of the drug product manufactured in the approved and proposed batch size for oral solid dosage forms as per compendium and validated dissolution test method (where applicable). 2. Comparative tabulated format of approved and proposed batch manufacturing formula. 3. Validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration the proposed batch size should be provided upon submission. 4. Release and shelf-life specifications of the drug product. 5. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product on a minimum of one production batch manufactured according to approved and proposed batch sizes and letter of undertaking to submit batch analysis data on the next one full production batch. 6. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action).

MaV-9	**Major change in the manufacturing process for drug product**
C	1. The change does not cause a negative impact on the quality, safety and efficacy of the drug product. 2. The manufacturing site remains unchanged. If there is a change in manufacturing site, MaV-4 is also applicable. 3. For minor change of the manufacturing process for non-sterile product, please refer to MiV-PA20/MiV-N11.
D	1. Description of the proposed manufacturing process and technical justification for the change. 2. Comparative dissolution profile data of at least one pilot/production batch of the drug product manufactured in the approved and proposed manufacturing process for oral solid dosage forms as per compendium and validated dissolution test method. 3. Validation scheme and/or report of the proposed manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration should be provided upon submission. 4. Copy of approved release and shelf-life specifications. Or, alternatively, copy of proposed release and shelf-life specifications that supports that the proposed process must lead to an identical or better product regarding all aspects of quality, safety and efficacy. 5. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product for a minimum of one production batch manufactured according to approved and proposed processes. 6. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 7. Justification for not submitting a new bioequivalence study according to ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies (where applicable).

MaV-10	**Qualitative or quantitative change of excipient** **a) For immediate release oral dosage forms (as per Level 2 and 3, Part III Components and Composition, SUPAC guideline)** **b) For modified release oral dosage forms** **c) For other critical dosage forms such as sterile preparations.**
C	1. Change will need to comply with the finished product specifications for example release and shelf-life specifications of the drug product remain unchanged, excluding product description except for update of product description with respect to appearance/odour/taste as a consequence of the change (where applicable). 2. Replacement of an excipient with a comparable excipient of the same functional characteristics. 3. The dissolution profile of the proposed product is comparable to that of the approved product. 4. Process validation scheme and/or report is available or validation of the manufacturing process has been successfully carried out according to protocol with at least three batches of the proposed product formula in accordance with the ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration. 5. For other qualitative or quantitative changes of excipient for immediate release oral dosage forms and other non-critical dosage forms, please refer to MiV-PA15.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. A declaration that the proposed excipient does not interfere with the drug product release and shelf-life specifications test method (where applicable). 3. Justification for the change must be given by appropriate development of pharmaceutics. 4. Comparative tabulated format of the approved and proposed product formulation with calculated changes highlighted (please state changes in the percentage of the proposed excipient out of the total target dosage form weight (where applicable). 5. Comparative dissolution profile data of at least one pilot/production batch of the drug product manufactured in the approved and proposed formulation for oral solid dosage forms as per compendium and validated dissolution test method (where applicable). 6. Revised batch manufacturing formula. 7. Validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration appropriate to the proposed change in product formula should be provided upon submission. 8. Revised ACTD Section P3.1 to P3.4 (where applicable). 9. Specifications of the proposed excipient. 10. For proposed excipients made of ruminants source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate or Bovine Spongiform Encephalopathy (BSE)-free cert issued from relevant authority of the issuing country and/or documentary evidence from the supplier (where applicable).

	11. Drug product release and shelf-life specifications. 12. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product on at least two production (or one production batch and two pilot batches) according to approved and proposed product formula. 13. Stability data as per ASEAN Guideline on Stability Study of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 14. Justification for not submitting a new bioequivalence study according to ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies (where applicable). 15. For quantitative and qualitative changes in preservative, results of Preservative Effectiveness Test (PET) at lowest specified preservative level (where applicable).
MaV-11	**Quantitative change in coating of tablets and/or size of capsule shell for modified release oral dosage form**
C	1. The dissolution profile of the proposed product is comparable to that of the approved product. 2. The release and shelf-life specifications of the drug product remain unchanged except for the weight and/or size (where applicable). 3. For quantitative change in coating of tablets or weight and/or size of capsule shell for immediate release oral solid dosage forms, please refer to MiV-PA16.
D	1. Revised draft of product label incorporating the proposed change (where applicable). 2. A declaration that the change does not interfere with the drug product release and shelf-life specifications test method. 3. Comparative dissolution profile data of at least one pilot/production batch of the drug product manufactured in the approved and proposed composition for oral solid dosage forms as per compendium and validated dissolution test method (where applicable). 4. Approved and proposed product and batch manufacturing formula. 5. Revised release and shelf-life specifications of the drug product. 6. Stability data as per ASEAN Guideline on Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 7. Justification for not submitting a new bioequivalence study according to the ASEAN Guidelines for The Conduct of Bioavailability and Bioequivalence Studies (where applicable).

MaV-12	**Change in primary packaging material for sterile product** **a) Qualitative and quantitative composition and/or** **b) Type of container and/or** **c) Inclusion of primary packaging material**
C	1. Release and shelf-life specifications of the drug product remain unchanged. 2. For change in the primary packaging material for non-sterile drug product, please refer to MiV-PA28.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Appropriate scientific data on proposed packaging (comparative data on permeability, e.g. moisture, O_2, CO_2). 3. Proof must be provided that no interaction between the content and the packaging material occurs (where applicable). 4. Validation scheme and/or report of the manufacturing and sterilization process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration appropriate to the proposed change in primary packaging material should be provided upon submission. 5. Comparative tabulated format of specifications of the approved and proposed primary packaging material. 6. Revised ACTD Sections P3 and/or P7 (where applicable). 7. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action).

MaV-13	**Change or addition of pack size/fill volume and/or change of shape or dimension of container or closure for sterile solid and liquid drug product**
C	1. The proposed pack size is consistent with the dosage regimen and duration of use as approved in the package insert. 2. The packaging material remains unchanged. 3. Release and shelf-life specifications of the drug product are not affected, except pack size/fill volume specification. 4. Change or addition of pack size/fill volume and/or change of shape or dimension of container or closure for non-sterile drug product, please refer to MiV-PA30.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Justification that the proposed pack size is consistent with the dosage regimen and duration of use as approved in the package insert. 3. Validation data of the manufacturing process, sterilization and container closure system (where applicable). 4. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action).
MaV-14	**Inclusion or replacement of the solvent/diluent for the drug product**
C	1. The proposed change does not result in any change in the dosage form, regimen, indication, method of administration of the product. 2. For deletion of the solvent/diluent, please refer to MiV-PA18. 3. For change of shelf-life and/or storage condition of the drug product after first opening and/or after dilution/reconstitution, please also refer to MaV-15/MiV-PA34 and/or MaV-16/MiV-PA35 (where applicable).
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation. 2. Documentary evidence to certify the manufacturing site of diluents/solvents complies with current applicable GMP standards (where applicable). 3. Batch numbering system (where applicable). 4. A letter of authorization from product owner to authorize the manufacturing site to manufacture and package the solvent/diluent (where applicable). 5. A declaration from the marketing authorization holder that the release and shelf-life specifications of drug product are not affected. 6. In addition to section P for the solvent/diluent and reconstitution stability data, section S is also required (where applicable).

MaV-15	**Extension of shelf-life of the drug product** **a) As a package for sale and/or** **b) After first opening and/or** **c) After dilution/reconstitution**
C	1. For (a) & (b) - The studies must show conformance to the approved shelf-life specification. 2. For (c)–The studies must show conformance to the approved shelf-life specification for the reconstituted product. 3. For reduction of shelf-life, please refer to MiV-PA34.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Technical justification for the proposed change (where applicable). 3. A letter of commitment from product owner or marketing authorization holder to inform users of the relevant change (where applicable). 4. Results of appropriate long-term stability studies covering the duration of proposed shelf-life of at least two pilot/production scale batches of the product in the authorized packaging material a) as a package for sale and/or b) after first opening and/or c) after the dilution/reconstitution 5. in accordance with the ASEAN Guidelines on Stability Study of Drug Product; results of appropriate microbiological testing should be included (where appropriate).
MaV-16	**Change of storage conditions of the drug product (Lowering from the approved storage condition)** **a) As a package for sale and/or** **b) After first opening and/or** **c) After dilution/reconstitution**
C	1. For (a) & (b) - The studies must show conformance to the approved shelf-life specification. 2. For (c) – The studies must show conformance to the approved shelf-life specification for the reconstituted product. 3. For change of storage condition (Increasing from the approved storage condition), please refer to MiV-PA35.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Technical justification for the proposed change. 3. Results of appropriate long-term stability studies covering the duration of approved shelf-life (at proposed storage condition) of at least two pilot/production scale batches of the product and in the authorized packaging material a) as a package for sale and/or b) after first opening and/or c) after the dilution/reconstitution in accordance with the ASEAN

	Guidelines on Stability Study of Drug Product, results of microbiological testing should be included (where appropriate).

MaV-17	**Major change in the manufacturing process of the drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]**
C	1. No adverse change in qualitative and/or quantitative impurity profile which would require further qualifications in safety studies. 2. The synthetic route is different. Refer to MiV-PA7 if the synthetic route remains unchanged. 3. Manufacturing process of drug substance does not use any materials of human/animal origin for which assessment is required of viral safety; unless otherwise justified. 4. Physicochemical characteristics and other relevant properties of drug substance remain unchanged. 5. Stability performance of drug substance remain unchanged. 6. If there are changes to the specification of drug substance, MiV-PA8 is also applicable.
D	1. Relevant ACTD section S1-S7, or both the open and closed part of the Drug Master File (closed part may be provided directly by manufacturer) with the Letter of Access or equivalent audit document/certification from reference country which is deemed appropriate by DDF. 2. Comparative tabulated format of the approved and proposed processes with changes highlighted (where available). 3. For sterile drug substance, process validation report (where applicable). 4. A letter of declaration from marketing authorization holder stating that no new impurities have been introduced at or above the accepted threshold for qualification of impurities or that there is no increase in the levels of impurities, which require further safety studies. 5. A letter of declaration from the marketing authorization holder stating that the specifications of the drug substance have not changed (where applicable). 6. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) for at least two pilot batches of the drug substance from the approved and proposed process. 7. A declaration from the marketing authorization holder that the relevant stability studies of the drug product in accordance with the ASEAN Guideline On Stability Study Of Drug Product will be started and that the relevant stability studies will be finalized; data should be provided only if outside specification (with proposed action). 8. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product of at least two batches (pilot/production scale) manufactured with the drug substance according to the approved and proposed processes.

8. Minor Variation Prior Approval

Minor Variation (MiV-PA)	
Prior Approval	
MiV-PA1	**Change of drug product name**
C	1. There is no change to the product (formulation, release and shelf-life specifications, manufacturing source and process) except for the product name change. 2. No confusion with another drug product either when spoken or written. 3. The proposed name does not (i) suggest greater safety or efficacy than supported by clinical data (ii) imply a therapeutic use (iii) imply superiority over another similar product and (iv) imply the presence of substance(s) not present in the product.
D	1. Revised draft package insert and labeling incorporating the proposed variation. 2. Updated Certificate of Pharmaceutical Product (CPP) (where applicable). 3. Official letter from product owner or marketing authorization holder authorizing the change of product name and committing to inform users of the relevant changes (where applicable). 4. A declaration from the marketing authorization holder that there is no other changes to the product/label except for the change of drug product name. 5. Trademark certificate (where applicable).
MiV-PA2	**Change of product labeling (in accordance to country specific labeling requirement)** Includes: a) Change of the layout/artwork without altering meaning. b) Addition/deletion/replacement of pictures, diagrams, bar code, logos and/or texts that do not imply an unapproved indication. c) Addition/strengthening of warnings, precautions, contraindications and/or adverse events/effects to the approved product labeling. d) Tightening of product's target population. e) Deletion of indication. f) Change of distributor's details.

C	1. Product labeling refers to Package Insert (PI), Patient Information Leaflet (PIL), unit carton label, inner label and/or blister strips. 2. The change is not a MaV and does not contain promotional information. For major change in product labeling, please refer to MaV-2.
D	1. Approved product labeling. 2. Proposed product labeling, a clean and annotated version highlighting the changes made. 3. Letter of declaration from the marketing authorization holder stating that no other changes on the label except for the intended change. 4. Relevant document/reference to support the changes (where applicable).

MiV-PA3	**Addition or replacement of the company or party responsible for batch release**
C	1. Only applicable for batch release. 2. The manufacturer of the drug product remains unchanged. 3. Method transfer from the approved to the proposed site or test laboratory has been successfully completed.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Proof that the proposed site is appropriately authorized (accredited by the authority) to be responsible for batch release such as a valid GMP certificate or CPP which covers the GMP certification. 3. Official letter from product owner authorizing the company/manufacturer to be responsible for batch release (where applicable).
MiV-PA4	**Addition or replacement of alternative manufacturer/site of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is available]**
C	1. Specifications of drug substances remain unchanged. 2. For change and/or addition of alternative manufacturer/site of drug substance where CEP is not available, please refer to MaV-3.

D	1. A valid European Pharmacopoeial Certificate of Suitability (CEP) for the drug substance, latest version, with all annexes issued by the European Directorate for the Quality of medicines (EDQM). 2. A letter of commitment from marketing authorization holder to conduct long term and accelerated stability studies for the drug product manufactured with the drug substance from the proposed manufacturing site, and report if any results fall outside shelf-life specifications (with proposed action) or when requested. 3. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) for at least two pilot batches of the drug substance from the approved and proposed manufacturing sites. 4. If the re-test period is not stated in the CEP, long term and accelerated stability data up to the proposed re-test period on two pilot batches of the drug substance manufactured from the proposed manufacturing sites should be provided.

MiV-PA5	**Change of batch size of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]**
C	1. The change does not affect the reproducibility of the process. 2. Specifications of drug substance remain unchanged. 3. For change of specification of drug substance where a CEP is available, please refer to MiV-PA12.
D	1. A letter of declaration from marketing authorized holder that the specifications of drug substance have not changed and the reproducibility of the process has not been affected 2. Certificate of analysis and/or batch analysis data with specification and results (in a comparative tabulated format) on a minimum of one production or pilot batch manufactured to both the approved and proposed batch sizes. Batch analysis data on the next two full production batches should be available on request or reported if outside specification (with proposed action). 3. Amended relevant ACTD Section S (where applicable).

MiV-PA6	**Change of in-process controls applied during the manufacture of the drug substance [including tightening and addition of new in-process test and where European Pharmacopoeial Certificate of Suitability (CEP) is not available]**
C	1. In-process limits are tightened or new tests are added. 2. The change is not a consequence of any commitment from previous assessments to review specification limits. 3. The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits. 4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way. 5. For change of specification of drug substance where a CEP is available, please refer to MiV-PA12.
D	1. A description of the analytical method and summary of validation data must be provided for all new analytical methods (where applicable). 2. Comparative tabulated format of the approved and proposed in-process controls and the relevant changes. 3. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of two production batches of the drug substance for all tests in the proposed specification (where applicable).

MiV-PA7	**Minor change of manufacturing process of the drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]**
C	1. No adverse change in qualitative and/or quantitative impurity profile which would require further qualifications in safety studies. 2. The synthetic route remains unchanged (for example, intermediates remain unchanged). Refer to MaV-17 if synthetic route is different. 3. Manufacturing process of drug substance does not use any materials of human/animal origin for which assessment is required of viral safety. 4. Physicochemical characteristics and other relevant properties of drug substance remain unchanged. 5. Specifications and stability performance of drug substance remain unchanged.
D	1. Drug Master File (DMF), or relevant updated drug substance (DS) section or equivalent/audit document.

	2. Comparative tabulated format of the approved and proposed processes with changes highlighted (where available). 3. For sterile drug substance, process validation report (where applicable). 4. A letter of declaration from marketing authorization holder stating that no new impurities have been introduced at or above the accepted threshold for qualification of impurities or that there is no increase in the levels of impurities, which require further safety studies. 5. A letter of declaration from the marketing authorization holder stating that the specifications of the drug substance have not changed. 6. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) for two batches of the drug substance. 7. A declaration from the marketing authorization holder that the relevant stability studies of the drug product in accordance with the ASEAN Guideline On Stability Study Of Drug Product have been started and that the relevant stability studies will be finalized; data should be provided only if outside specification (with proposed action). 8. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product of at least two batches (pilot/production scale) manufactured with the drug substance according to the approved and proposed processes.

MiV-PA8	**Change of the specification of drug substance** **a) Specification limits are tightened** **b) Addition of new test parameter and limits**
C	1. This is only applicable for drug substances which are non-compendial and generic drug substances without European Pharmacopoeial Certificate of Suitability (CEP)

	2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns; unless otherwise justified. 3. Test procedures remain unchanged, or changes in the test procedure are minor. 4. For (b) - applicable to non-compendial method only. 5. For change of specification of drug substance where a CEP is available, please refer to MiV-PA12. 6. For widening of specification limits and deletion of test parameter and limits of drug substance, please refer to MaV-6.
D	**(a) Specification limits are tightened** 1. Technical justification for the change. 2. Comparative tabulated format of the approved and proposed specification of drug substance with changes highlighted. 3. Comparative batch analysis data of the drug substance for all tests in the proposed specification for two pilot or production scale batches. **(b) Addition of new test parameter and limits** In addition to the above documents, 4. Description of any new analytical method and summary of the validation data.
MiV-PA9	**Change of the test procedure of non-compendial drug substance**
C	1. Results of method validation show proposed test procedure to be at least equivalent to the approved procedure. 2. For change of specification of drug substance where a CEP is available, please refer to MiV-PA12.
D	1. Description of the proposed test procedure with a summary of change(s) from the approved test procedure. 2. Appropriate verification/validation data of the proposed test procedure. 3. Specification of the drug substance. 4. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) for at least two pilot batches of the drug substance from the approved and proposed test procedure.

MiV-PA10	**Change of shelf-life or re-test period for drug substance**
C	1. The stability studies must show compliance with specification. 2. There is no change in storage condition. 3. For change of specification of drug substance where a CEP is available, please refer to MiV-PA12.
D	1. Specifications of the drug substance. 2. Stability data of the drug substance should be presented on at least two pilot or production scale batches of the proposed shelf-life or retest period.
MiV-PA11	**Change of storage condition for drug substance**
C	1. The stability studies must show compliance with specification. 2. There is no change in shelf-life/re-test period. 3. For change of specification of drug substance where a CEP is available, please refer to MiV-PA12.
D	1. Specifications of the drug substance. 2. Stability data of the drug substance should be presented on at least two pilot or production scale batches of the proposed storage condition.
MiV-PA12	**Revision of European Pharmacopoeial Certificate of Suitability (CEP) of drug substance**
C	None
D	1. A valid European Pharmacopoeial Certificate of Suitability (CEP) for the drug substance, latest version, with all annexes issued by EDQM. 2. If this change is due to drug substance specification change, a declaration from the applicant that the relevant stability studies of the drug product in accordance with ASEAN Guideline On Stability Study Of Drug Product have been started and that the relevant stability studies will be finalized; data should be provided only if outside specification (with proposed action). 3. Specifications of drug substance (where applicable). 4. Certificate of analysis and/or results of batch analysis data (in a comparative tabulated format) from the drug substance manufacturer* demonstrating compliance with the Ph. Eur monograph and including additional test/limits listed on the CEP (where applicable). 5. Additional data to address any relevant parameter(s) not addressed in the CEP such as stability data (S7), if a re-test period is not stated on the CEP and

	physicochemical characteristics (e.g. particle size, polymorphism etc), if applicable. * If the drug substance manufacturer is CEP certified and the drug product manufacturer claims otherwise (USP, JP, In-house etc), data covering S4.1 to S4.5 from the drug product manufacturer should be submitted.

MiV-PA13	**Change of batch size of non-sterile drug product**
C	1. The change does not affect consistency of production. 2. The product formulation remains unchanged. 3. Process validation scheme and/or report is available or validation of the manufacturing process has been successfully carried out according to protocol with at least three batches at the proposed proposed batch size in accordance with the ASEAN Guideline on Submission of Manufacturing Process Validation Data For Drug Registration. 4. Release and shelf-life specifications of drug product remain unchanged. 5. This is applicable to change of batch size up to 10-fold compared to the approved batch size. 6. For change of batch size for sterile products, please refer to MaV-7 and for change of batch size more than 10-fold compared to the approved batch size, please refer MaV-8.
D	1. Comparative tabulated format of approved and proposed batch manufacturing formula. 2. Validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration appropriate to the proposed batch size should be provided upon submission. 3. Revised ACTD Section P3.1-3.4 (where applicable). 4. Release and shelf-life specifications of the drug product. 5. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product on a minimum of one production batch manufactured according to approved and proposed batch sizes and letter of undertaking to submit batch analysis data on the next one full production batch. 6. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action).
MiV-PA14	**Reduction or removal of overage**

C	1. Changes of approved manufacturing overages of drug substance only. 2. Release and shelf-life specifications of drug product remain unchanged.
D	1. Justification for the change. 2. Comparative tabulated format of approved and proposed batch manufacturing formula. 3. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) for two batches of the finished product. 4. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action).

MiV-PA15	**Qualitative and/or quantitative change of excipient** **a. For immediate release oral dosage forms (as per Level 1, Part III Components and Composition, SUPAC guideline)** **b) b) For other non-critical dosage forms eg. oral liquid, external preparation.**
C	1. Replacement of an excipient with a comparable excipient of the same functional characteristics (where applicable). 2. The dissolution profile of the proposed product is comparable to that of the approved product. 3. Process validation scheme and/or report is available or validation of the manufacturing process has been successfully carried out according to protocol with at least three batches of the proposed product formula in accordance with the ASEAN Guideline on Submission of Manufacturing Process Validation Data For Drug Registration. 4. Release and shelf-life specifications of the drug product remain unchanged; except for the update of product description with respect to appearance/odour/taste as a consequence of the change (where applicable). 5. For qualitative or quantitative change of excipient for immediate release (Level 2 and 3 change as per SUPAC) and modified release oral dosage forms and other critical dosage forms, please refer to MaV-10.

D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. A declaration that the proposed excipient does not interfere with the drug product release and shelf-life specifications test method (where applicable). 3. Justification for the change must be given by appropriate development of pharmaceutics. 4. Comparative tabulated format of the approved and proposed product formulation with calculated changes highlighted (please state changes in the percentage of the proposed excipient out of the total target dosage form weight, where applicable). 5. Comparative dissolution profile data of at least one pilot/production batch of the drug product manufactured in the approved and proposed formulation for oral solid dosage forms as per compendium and validated dissolution test method (where applicable). 6. Revised batch manufacturing formula. 7. Validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration appropriate to the proposed change in product formula should be provided upon submission (where applicable). 8. Revised ACTD Section P3.1-3.4 (where applicable). 9. Specifications of the proposed excipient. 10. For proposed excipients made of ruminants source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate or Bovine Spongiform Encephalopathy (BSE)-free cert issued from relevant authority of the issuing country and/or documentary evidence from the supplier (where applicable). 11. Release and shelf-life specifications. 12. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product of at least two production (or one production batch and two pilot batches) according to approved and proposed product formula. 13. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 14. Justification for not submitting a new bioequivalence study according to the ASEAN Guidelines For The Conduct of Bioavailability and Bioequivalence Studies. 15. For quantitative and qualitative changes in preservative, results of Preservative Effectiveness Test (PET) at lowest specified preservative level (where applicable).
MiV-PA16	**Quantitative change in coating of tablets and/or size of capsule shell for immediate release oral solid dosage form**
C	1. The dissolution profile of the proposed product is comparable to that of the approved product.

	2. The product release and shelf-life specifications of the drug product remain unchanged except for the weight and/or size. 3. For quantitative change in coating of tablets and/or size of capsule shell for modified release oral solid dosage forms please refer to MaV-11.
D	1. Revised draft of product label incorporating the proposed change (where applicable). 2. A declaration from marketing authorization holder that the change does not interfere with the drug product release and shelf-life specifications test method. 3. Comparative tabulated format of approved and proposed product and batch manufacturing formula. 4. Comparative dissolution profile data of at least one pilot/production batch of the drug product manufactured in the approved and proposed composition for oral solid dosage forms as per compendium and validated dissolution test method (where applicable). 5. Revised release and shelf-life specifications of the drug product. 6. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). Except for the change in weight and/or size of capsule shell, a letter of declaration from the applicant that the relevant stability studies of the drug product in accordance with ASEAN Guideline on Stability Study of Drug Product have been started will suffice. 7. Justification for not submitting a new bioequivalence study according to the ASEAN Guidelines For The Conduct of Bioavailability and Bioequivalence Studies (where applicable).

MiV-PA17	**Change of the colouring agent/flavouring agent/capsule shell colour of the product**
C	1. Same functional characteristics, no change in dissolution profile for solid oral dosage forms. 2. The proposed colouring agents /flavouring agents/capsule shell must not have been rejected for pharmaceutical use. 3. The release and shelf-life specifications of the drug product remain unchanged, except for the update of product description with respect to appearance/odour/taste as a consequence of the change (where applicable). 4. If there is a change to the source of capsule shell, MiV-PA23 is also applicable.

D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. A declaration that the proposed colouring agent/flavouring agent/capsule shell colour does not interfere with the drug product release and shelf-life specifications test method. 3. A letter of commitment from product owner or marketing authorization holder to inform users of the relevant change (where applicable). 4. Revised product formulation and batch manufacturing formula. 5. Qualitative and quantitative information of the approved and proposed colouring agent/flavouring agent/capsule shell colour in a comparative table. 6. For proposed excipients made of ruminants source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate or Bovine Spongiform Encephalopathy (BSE)-free certificate issued from relevant authority of the issuing country and/or documentary evidence from the supplier (where applicable). 7. Revised release and shelf-life specifications of the drug product. 8. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 9. Certificate of Analysis of proposed coloring agent/flavoring agent/capsule shell (where applicable).

MiV-PA18	**Deletion of the solvent/diluent for the drug product**
C	1. The proposed change does not result in any change in the dosage form, regimen, indication, method of administration of the product.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Justification for the deletion of the solvent/diluent, including a statement regarding alternative means to obtain the solvent/diluent. 3. Amended relevant ACTD Section P (where applicable).
MiV-PA19	**Change of in-process controls applied during the manufacture of the drug product (including tightening and addition of new in-process test)**
C	1. Release and shelf-life specifications of drug product remain unchanged.

	2. The change is not a consequence of any commitment from previous assessments to review specification limits. 3. The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits. 4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
D	1. Comparative tabulated format of approved and proposed in-process controls. 2. A description of the analytical methodology and summary of validation data must be provided for all new analytical methods (where applicable). 3. Proposed in-process specifications together with justification and relevant process validation data. 4. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product of at least two production/pilot batches.

MiV-PA20	**Minor change of the manufacturing process for non-sterile product**
C	1. The manufacturing site remains unchanged. 2. The overall manufacturing principle remains unchanged. 3. The change does not cause negative impact on the quality, safety and efficacy of the drug product. 4. The dissolution profile of the proposed product is comparable to that of the approved product. 5. Release and shelf-life specifications of drug product remain unchanged. 6. For major change in the manufacturing process for drug product, please refer to MaV-9/MiV-N11.
D	1. Comparative dissolution profile data of at least one pilot/production batch of the drug product manufactured in the approved and proposed manufacturing process for oral solid dosage forms as per compendium and validated dissolution test method (where applicable). 2. Description of the proposed manufacturing process and technical justification for the change. 3. Comparative tabulated format of approved and proposed process with changes highlighted. 4. For semi solid and suspension products, validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of

	Manufacturing Process Validation Data for Drug Registration should be provided upon submission. 5. Copy of approved release and shelf-life specifications. Or, alternately, copy of revised release and shelf-life specifications that supports that the proposed process must lead to an identical or better product regarding all aspects of quality, safety and efficacy. 6. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product on a minimum of one batch manufactured to both the approved and the proposed process; batch analysis data on the next two full production batches should be made available upon request. 7. A declaration from the marketing authorization holder that the relevant stability studies of the drug product in accordance with the ASEAN Guideline on Stability Study of Drug Product have been started and that the relevant stability studies will be finalized; data should be provided only if outside specification (with proposed action). 8. Justification for not submitting a new bioequivalence study according to the current Bioavailability and Bioequivalence guidance (where applicable).

MiV-PA21	**Change of specifications of non-compendial excipient** **a) Specification limits are tightened/widened** **b) Addition/replacement/deletion of test parameter and limits**
C	1. Release and shelf-life specifications of drug product remain unchanged. 2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns; unless otherwise justified. 3. Applicable to non-compendial excipients. For compendial excipients, please refer to MiV-N9.
D	1. Description of new method and summary of analytical validation (applicable for addition/replacement of new parameter). 2. Comparative tabulated format of the approved and proposed specification of the excipient with changes highlighted. 3. Certificate of analysis of the excipient for all tests in the proposed specification.
MiV-PA22	**Change of a test procedure for an excipient, including replacement of an approved test procedure by a new test procedure**
C	1. Appropriate method validation studies have been performed in accordance with the ASEAN Guidelines For Validation of Analytical Procedures. 2. Results of method validation show proposed test procedure to be at least equivalent to the approved procedure. 3. There have been no changes of the total impurity limits. 4. Only applicable to the approved test parameters. 5. No new unqualified impurities are detected. 6. This applies for non-compendial excipient. For compendial excipients, please refer to MiV-N9.
D	1. Description of the proposed analytical methodology with a comparative tabulation of the changes. 2. For quantitative test change, comparative analytical validation results showing that the approved and proposed tests are equivalent.

MiV-PA23	**Change in the source of empty hard capsule**
C	1. The change is from TSE-risk material to vegetable-sourced or synthetic empty hard capsules or vice versa. 2. The formulation and manufacturing process of drug product remain unchanged. 3. Not applicable to change from hard capsule to soft gel. 4. Excipient and finished product release and shelf-life specifications remain unchanged.
D	1. A letter of declaration from the manufacturer or the marketing authorization holder of the material that it is purely of vegetable, animal or synthetic origin. 2. Technical specifications and composition of the empty hard capsule of the proposed source. 3. For empty hard capsule made of ruminants source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate or Bovine Spongiform Encephalopathy (BSE)-free cert issued from relevant authority of the issuing country and/or documentary evidence from the supplier. 4. Comparative dissolution profile data of at least one pilot/production batch of the drug product using hard capsule between the two sources for oral solid dosage as per as per compendium and validated dissolution test method (where applicable). 5. Certificate of Analysis of the empty hard capsule of the proposed source. 6. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action).
MiV-PA24	**Change of release and shelf-life specifications of the drug product** **a) Specification limits are tightened** **b) Addition of new test parameter and limits**

C	1. Applicable to non-compendial method. 2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns; unless otherwise justified. 3. The test methods remain unchanged or changes in the test methods are minor. 4. If there are changes to the test procedure, MiV-PA27 is also applicable. 5. For widening of specification limits and deletion of test parameter and limits of drug product, please refer to MaV-6.
D	**(a) Specification limits are tightened** 1. Technical justification for the change. 2. Comparative tabulated format of the approved and proposed release and shelf-life specifications of the drug product with changes highlighted. 3. Certificate of analysis and/or batch analysis (in a comparative tabulated format) of the drug product for all tests in the proposed specification of at least two batches. **(b) Addition of new test parameter and limits** In addition to the above documents: 4. Description of any new method and summary of analytical validation data for non-compendial method. 5. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). (where applicable).

MiV-PA25	**Change of imprints, bossing or other markings on tablets or printing on capsules including addition or change of inks used for product marking**
C	**(a) Except score/break-line** 1. Proposed markings do not cause confusion with other registered products. 2. Any ink proposed must comply to relevant pharmaceutical legislation or of food grade and not a listed banned substance. 3. Release and shelf-life specifications of the drug product remain unchanged except for appearance. **(b) On score/break-line** In addition to the above conditions, 4. Score/break-line is not meant for cosmetic purpose.

	5. Applicable to addition or removal of score/break-line.
D	**<u>(a) Except score/break-line</u>** 1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. A letter of commitment from product owner or marketing authorization holder to inform users of the relevant change (where applicable). 3. Details and specifications of the proposed inks (where applicable). 4. Detailed drawing or written description of the approved and proposed imprint/bossing/markings. 5. Certificate of analysis of ink/printing material (pharmaceutical grade and of food grade) (where applicable). 6. Release and shelf-life specifications of the drug product with the proposed product description. **<u>(b) On score/break-line</u>** In addition to the above documents, 7. Justification for the change (i.e. change in dosing regimen). 8. Data on test of uniformity of the subdivided parts of the tablets at release as conformed to compendial requirement. 9. Certificate of analysis and/or batch analysis (in a comparative tabulated format) of the drug product of two production/pilot scale batches.

MiV-PA26	**Change of dimensions and/or shape of tablets, capsules, suppositories or pessaries without change in qualitative and quantitative composition and mean mass** **a) Immediate release oral solid dosage form, suppositories and pessaries** **b) Other than immediate release oral solid dosage forms, suppositories and pessaries.**
C	1. If appropriate, the dissolution profile of the proposed product is comparable to that of the approved product. 2. Release and shelf-life specifications of the drug product remain unchanged except for dimension and/or shape.

D	**(a) Immediate release oral solid dosage form, suppositories and pessaries** 1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Detailed drawing or written description of the approved and proposed appearance. 3. Comparative dissolution profile data of at least one pilot/production batch of the drug product manufactured in the approved and proposed dimensions/shape for oral solid dosage forms as per as per compendium and validated dissolution test method (where applicable). 4. For scored tablets, data on test of uniformity of the subdivided parts of tablets at release as conformed to compendial requirement. 5. Release and shelf-life specifications of the drug product with proposed dimension and/or shape. **(b) Other than immediate release oral solid dosage forms, suppositories and pessaries** In addition to the above condition, 6. Justification for not submitting a new bioequivalence study according to the ASEAN Guidelines For The Conduct of Bioavailability and Bioequivalence Studies (where applicable).

MiV-PA27	**Change in the test procedure of the drug product (including replacement or addition of a test procedure)**
C	1. Drug product specifications are not adversely affected unless the specifications are tightened. 2. Results of method verification/validation show proposed test procedure to be at least equivalent to the approved procedure. 3. The change should not be the result of unexpected events arising during manufacture or because of stability concerns; unless otherwise justified.
D	1. Justification for the proposed change. 2. Comparative tabulated format of the approved and proposed release and shelf-life specifications of the drug product. 3. Description of the analytical methodology. 4. Appropriate verification/validation data and comparative analytical results between the approved and proposed test. 5. Certificate of analysis and/or batch analysis (in a comparative tabulated format) of the finished product of two production batches when made available.
MiV-PA28	**Change in primary packaging material for non-sterile product** **a) Qualitative and quantitative composition and/or** **b) Type of container and/or** **c) Inclusion of primary packaging material**
C	1. The proposed packaging material must be at least equivalent to or better than the approved material in respect of its relevant properties. 2. Release and shelf-life specifications of drug product remain unchanged. 3. For change in the primary packaging material for sterile drug product, please refer to MaV-12.
D	4. Revised drafts of the package insert incorporating the proposed variation (where applicable). 5. Justification for the change in packaging material and appropriate scientific studies on the proposed packaging. 6. For semi-solid and liquid dosage forms, proof must be provided that no interaction between the content and the packaging material occurs (e.g. no

	migration of components of the proposed material into the content and no loss of components of the product into the pack). 7. Comparative tabulated format of the approved and proposed specifications of the primary packaging material (where applicable). 8. Revised ACTD Sections P3 and/or P7 (where applicable). 9. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action).

MiV-PA29	**Addition or replacement of a manufacturer for secondary packaging**
C	None
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Proof that the proposed site is appropriately authorized (accredited by the authority) for the packaging activity concerned such as a valid GMP certificate and/or CPP which covers the GMP certification. 3. Official letter from product owner authorizing the proposed manufacturer or packager to perform secondary packaging (where applicable).
MiV-PA30	**Change of pack size/fill volume and/or change of shape or dimension of container or closure for non-sterile product**
C	1. The change only concerns the same packaging type and material. 2. The proposed pack size is consistent with the dosage regimen and duration of use as approved in the package insert. 3. Change in the dimension of the primary packaging (where applicable). 4. Release and shelf-life specifications of the drug product remain unchanged. 5. For change of pack size/fill volume and/or change of shape or dimension of container or closure for sterile solid and liquid drug product, please refer to MaV-13.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).

	2. Justification for the proposed pack size. 3. Revised ACTD Sections P3 and/or P7 (where applicable). 4. A declaration from the marketing authorization holder that the relevant stability studies of the drug product in accordance with the ASEAN Guideline on Stability Study of Drug Product have been started and that the relevant stability studies will be finalized; data should be provided only if outside specification (with proposed action).

MiV-PA31	**Change of outer carton pack sizes for a drug product**
C	1. Primary packaging materials remain unchanged. 2. No other changes except for the change of outer carton pack sizes for a drug product. 3. The remaining pack sizes are adequate to accommodate the dosing regimen as per the approved product labeling.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Letter of declaration from the marketing authorization holder stating that no other changes except for the change of outer carton pack sizes for a drug product.
MiV-PA32	**Change in any part of the (primary) packaging material not in contact with the finished product formulation such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used)**
C	1. The change does not concern a part of the packaging material, which affects the delivery, use, safety or stability of the finished product.
D	1. Amendment of the relevant section(s) of the dossier (presented in the ACTD format), including revised product labeling as appropriate.
MiV-PA33	**Addition or replacement of measuring device for oral liquid dosage forms and other dosage form**
C	1. The size and where applicable, the accuracy of the proposed measuring device must be compatible with the approved posology. 2. The proposed device is compatible with the drug product.
D	1. Revised draft of the package insert and labeling incorporating the proposed variation (where applicable). 2. Description of the device (including a drawing; where applicable). 3. The composition of the device material. Where applicable the materials should comply with the pharmacopoeia. 4. Justification that size and accuracy of the device are adequate for the posology as approved in the product labeling.

	5. Data on test of uniformity of delivered dose as per compendium.

MiV-PA34	**Reduction of shelf-life of the drug product** **a) As a package for sale and/or** **b) After first opening and/or** **c) After dilution/reconstitution**
C	1. For (a) & (b) - The studies must show conformance to the approved shelf-life specification. 2. For (c) – The studies must show conformance to the approved shelf-life specification for the reconstituted product. 3. For extension of shelf-life, please refer to MaV-15.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Technical justification for the proposed change(where applicable). 3. A letter of commitment from product owner or marketing authorization holder to inform users of the relevant change (where applicable). 4. Results of appropriate long term stability studies covering the duration of proposed shelf-life of at least two pilot/production scale batches of the product in the authorized packaging material a) as a package for sale and/or b) after first opening and/or c) after the dilution/reconstitution in accordance with the ASEAN Guidelines on Stability Study of Drug Product; results of appropriate microbiological testing should be included (where appropriate).
MiV-PA35	**Change of storage conditions of the drug product (Increasing from the approved storage condition)** **a) As a package for sale and/or** **b) After first opening and/or** **c) After dilution/reconstitution**

C	1. For (a) & (b) - The studies must show conformance to the approved shelf-life specification. 2. For (c) – The studies must show conformance to the approved shelf-life specification for the reconstituted product. 3. For change of storage condition (lowering from the approved storage condition), please refer to MaV-16. 4. General precautionary statements on storage conditions in product labeling may be included but should not be used to conceal stability problems.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Technical justification for the proposed change. 3. Results of appropriate long term stability studies covering the duration of approved shelf-life (at proposed storage condition) of at least two pilot/production scale batches of the product and in the authorized packaging material a) as a package for sale and/or b) after first opening and/or c) after the dilution/reconstitution in accordance with the ASEAN Guidelines on Stability Study of Drug Product, results of microbiological testing should be included (where appropriate). 4. Data on photosensitivity and/or moisture sensitivity test on drug product (where applicable).

MiV-PA36	**Addition or replacement of alternative site for primary packaging (direct contact with drug product) for non-sterile product**
C	1. No other changes except for the addition or replacement of alternative site for primary packaging (direct contact with drug product). 2. For addition or replacement of alternative site for primary packaging (direct contact with drug product) for sterile product, please refer to MaV-5.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Proof that the proposed site is appropriately authorized for the packaging activity of the pharmaceutical form concerned such as a valid GMP Certificate and/or a CPP which covers GMP certification. 3. In case of a contract primary packager, letter of appointment and letter of acceptance for the proposed site to package the product and stating the types of activity to be performed by the packager (where applicable). 4. Validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration appropriate to the proposed change of alternative site for primary packaging (where applicable). 5. Holding time studies testing of bulk pack during storage and transportation between the bulk production site to primary packager (where applicable).

	6. A letter of commitment from marketing authorization holder to conduct long term and accelerated stability studies for the drug product packed at the proposed site, and report if any results fall outside shelf-life specifications (with proposed action) or when requested.
MiV-PA37	**Addition or replacement of the company or party responsible for quality control testing site (where applicable)**
C	1. Only applicable for quality control testing site. 2. The manufacturer of the drug product remains unchanged. 3. Method transfer from the approved to the proposed site or test laboratory has been successfully completed.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Documentary evidence that the proposed quality control testing site is appropriately accredited. 3. Official letter from product owner authorizing the company to be responsible for quality control testing site (where applicable). 4. Analytical method transfer data (where applicable).

9. Minor Variation Notification

Minor Variation (MiV-N)	
Notification	
MiV-N1	**Change in name and/or address (for example: postal code, street name) of the marketing authorization holder** [Note: DDF reserves the right to re-categorize this variation as MiV-PA, if deemed necessary]
C	1. The name change refers to the renaming of a company or organization. 2. The change does not include transfer of marketing authorization to another company.

	3. For change on the part of marketing authorization holder in product labeling only. Please refer to MaV-2 and MiV-PA2 if other parts are involved.
D	1. Revised draft package insert and labeling incorporating the proposed variation (where applicable). 2. Letter by the product owner authorizing the proposed name of marketing authorization holder to hold the product license. 3. Official document from the relevant authority confirming the change with the proposed name and/or address.
MiV-N2	**Change of product owner**
C	1. The marketing authorization holder remains unchanged. 2. The manufacturing site remains unchanged.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Declaration on the transfer of ownership between the approved and proposed product owner. 3. Official letter from the proposed product owner declaring the change, and authorizing the local license holder to be responsible for the product license. 4. If the proposed product owner is not the manufacturer of the drug product, an official letter by the proposed product owner authorizing the manufacturer to manufacture the drug product on its behalf. 5. If the proposed product owner is not the manufacturer of the drug product, letter of acceptance from the manufacturer that it will be held responsible for manufacturing and ensuring the efficacy, quality and safety aspect of the drug product.

MiV-N3	**Change in ownership of manufacturer** [Note: DDF reserves the right to re-categorize this variation as MiV-PA, if deemed necessary]
	1. The manufacturing site remains unchanged.

C	2. No other changes except for the change in ownership of manufacturer.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Letter of justification on the transfer of ownership such as a valid GMP certificate. 3. Official letter stating the transfer of ownership to the proposed manufacturer (where applicable). 4. In case of a contract manufacturer, official letter from product owner declaring the change and authorizing the proposed manufacturer to manufacture the drug products on its behalf. 5. In case of a contract manufacturer, letter of acceptance from the proposed manufacturer that it will be held responsible for manufacturing and ensuring the efficacy, quality and safety aspect of the drug product.
MiV-N4	**Change of the name or address (for example: postal code, street name) of the manufacturer of drug product** [Note: DDF reserves the right to re-categorize this variation as MiV-PA, if deemed necessary]
C	1. The manufacturing site remains unchanged. 2. No other changes except for the change of the name and/or address of a manufacturer of the drug product. 3. Not applicable to the case in which it involves change in ownership of the manufacturer. For change in ownership of manufacturer, please refer MiV-N3.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. A valid GMP certificate, CPP which covers the GMP certification or official document from relevant authority confirming the proposed name and/or address. 3. Official letter from product owner authorizing the manufacturer with proposed name/address to manufacture the drug product.

MiV-N5	**Change of the name or address (for example: postal code, street name) of the company or manufacturer responsible for batch release** [Note: DDF reserves the right to re-categorize this variation as MiV-PA, if deemed necessary]
C	1. The manufacturer of the drug product remains unchanged. 2. The batch release site remains unchanged. 3. Not applicable to the case in which it involves change in ownership of the manufacturer. For change in ownership of manufacturer, please refer MiV-N3.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. A valid GMP certificate CPP which covers the GMP certification or official document from relevant authority confirming the proposed name or address (where applicable). 3. Official letter from product owner authorizing company/manufacturer with proposed name/address responsible for batch release. 4. A declaration from the marketing authorization holder that the change does not involve change of batch release site.
MiV-N6	**Change of the name and/or address (for example: postal code, street name) of a manufacturer of the drug substance**
C	1. The manufacturing site of the drug substance remains unchanged. 2. No other changes except for the change of the name and/or address of a manufacturer of the drug substance.
D	1. Updated information of the manufacturer of the drug substance. 2. Official document/evidence where applicable.
MiV-N7	**Withdrawal/deletion of the alternative manufacturer(s) (for drug substance and/or drug product and/or packager)**
C	1. An alternative manufacturer is registered.

D	1. Reason for withdrawal/deletion.

MiV-N8	**Renewal of European Pharmacopoeial Certificate of Suitability (CEP)**
C	1. Only applicable if the renewal of CEP does not involve any variation.
D	1. A valid European Pharmacopoeial Certificate of Suitability (CEP) for the drug substance, latest version, with all annexes issued by EDQM.
MiV-N9	**Change of release and/or shelf-life/re-test specifications and/or test procedure of the drug product and/or drug substance and/or excipient, following the updates in the compendium**
C	1. Applicable to compendial specifications and/or test procedure only. 2. Change is made exclusively to comply with an update of the relevant monograph of the compendium.
D	1. Tabulation of the approved and proposed release and/or shelf-life/re-test specifications and/or test procedure of the drug product with changes highlighted. 2. Batch analysis data (in comparative tabulated format) of the drug product for all tests in the proposed specification of at least two batches and/or certificate of analysis of excipient and/or drug substance. 3. Revised release and/or shelf-life/re-test specifications. 4. For change in test procedure, appropriate verification data of the proposed test procedure (where applicable).
MiV-N10	**Deletion of pack size for a product**
C	1. The remaining pack sizes are adequate to accommodate the dosing regimen as per the approved product labeling. 2. For addition of pack size for sterile and non-sterile products, please refer to MaV-13 and MiV-PA30 respectively. For change in the outer carton pack size, please refer to MiV-PA31.

D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Reason for deletion.

MiV-N11	**Minor change in the manufacturing process of an immediate release solid oral dosage form, semi solid or oral solutions**
C	1. The change, as per Level 1, Part VI Manufacturing, SUPAC Guideline. 2. No change in qualitative and quantitative impurity profile or in physico-chemical properties. 3. The manufacturing principle including the single manufacturing steps remain unchanged, e.g. processing intermediates and there are no changes to any manufacturing solvent used in the process. 4. The approved process has to be controlled by relevant in-process controls and no changes (widening or deletion of limits) are required to these controls. 5. The specifications of the finished product or intermediates are unchanged. 6. The proposed process must lead to an identical product regarding all aspects of quality, safety and efficacy. 7. Relevant stability studies in accordance with the relevant guidelines have been started with at least one pilot scale or production scale batch and at least three months stability data are at the disposal of the applicant. Assurance is given that these studies will be finalized and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

D	1. Amendment of the relevant section(s) of the dossier, as appropriate, including a direct comparison of the approved process and the proposed process. 2. For semi-solid and liquid products in which the active substance is present in non-dissolved form: appropriate validation of the change including microscopic imaging of particles to check for visible changes in morphology; comparative size distribution data by an appropriate method. 3. For solid dosage forms: dissolution profile data of one representative production batch and comparative data of the last three batches from the previous process; data on the next two full production batches should be available on request or reported if outside specification (with proposed action). 4. Justification for not submitting a new bioequivalence study) according to the ASEAN Guidelines For The Conduct of Bioavailability and Bioequivalence Studies (where applicable). 5. Copy of approved release and shelf life specifications. 6. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) on a minimum of one batch manufactured to both the approved and the proposed process. Batch analysis data on the next two full production batches should be made available upon request and reported by the marketing authorization holder if outside specification (with proposed action). 7. A declaration from the marketing authorization holder that the relevant stability studies of the drug product will be started and that the relevant stability studies will be finalized; data should be provided only if outside specification (with proposed action).

Chapter J Annexes

Annex A: Quality Overall Summary (QOS)

Key to abbreviations

NCE = New Chemical Entity
Biotech = Biotechnological Products
MaV = Major Variations
MiV = Minor Variations
G = Generics
* = if required

For NCE and Biotech requirements please refer to the relevant ICH Guidelines.

Section B: Quality Overall Summary (QOS)

No.	PARAMETERS	COMPONENTS	REQUIREMENTS				
			NCE	BIOTECH	MaV	MiV	G
S	DRUG SUBSTANCE						
S1	General Information						
	1.1. Nomenclature	− Information from the S1	v	v	v*		v
	1.2. Structure	Structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass.	v				v
		Schematic amino acid sequence indicating glycosylation sites or other post- translational modifications and relative molecular mass as appropriate		v			
		Compendial requirement or equivalent information from the manufacture					v
	1.3. General Properties	Physico chemical characteristics and other relevant properties including biological activity for biotech	v	v	v*		v
S2	Manufacture						
	2.1. Manufacturer(s)	Name and address of the manufacturer (s).	v	v			v
	2.2. Description of Manufacturing	− The description of the drug substance manufacturing	v	v			

No.	PARAMETERS	COMPONENTS	REQUIREMENTS				
			NCE	BIOTECH	MaV	MiV	G
	Process and Process Controls	process and process control that represents the applicant's commitment for the manufacture of the drug substances.					
		− Information on the manufacturing process, which typically starts with a vial(s) of the cell bank, and includes cell culture, harvest(s), purification and modification reaction, filling, storage and shipping conditions.		v			
	2.3. Control of Materials	− Starting materials, solvents, reagents, catalysts, and any other materials used in the manufacture of the drugs substance indicating where each material is used in the process. Tests and acceptance criteria of these materials.	v	v			
		− Control of source and starting materials of biological origin.		v			
		− Source, history and generation of the cell substrate.		v			
		− Cell banking system, characterization and testing.		v			
		− Viral safety evaluation		v			
	2.4. Controls of Critical Steps and Intermediates	− Critical steps: Tests and acceptance criteria, with justification including experimental data, performed at critical steps of the manufacturing process to ensure that the process is controlled.	v	v			
		Intermediates: Specifications and analytical procedure, if any, for intermediates isolated during the process.	v	v			
		− Stability data supporting storage conditions.		v			
	2.5. Process	Process validation and/or	v	v			

No.	PARAMETERS	COMPONENTS	REQUIREMENTS				
			NCE	BIOTECH	MaV	MiV	G
	Validation and/or Evaluation	evaluation studies for aseptic processing and sterilization.					
	2.6. Manufacturing Process Development	− Description and discussion of significant changes made to the manufacturing process and/or manufacturing site of the drug substance used in producing non- clinical, clinical, scale-up, pilot and if available, production scale batches.	v				
		− The development history of the manufacturing process as described in S 2.2		v			
S3	Characterization						
	3.1. Elucidation of Structure and other characteristics	Confirmation of structure based on e.g. synthetic route and spectral analyses.	v				
		− Compendial requirements or appropriate information from the manufacturer					v
		− Details on primary, secondary and higher- order structure and information on biological activity, purity and immunochemical properties (when relevant).		v			
	3.2. Impurities	− Summary of impurities monitored or tested for during and after manufacture of drug substance	v	v			
		− Compendial requirements or appropriate information from the manufacturer					v
S4	Control of Drug Substance						
	4.1. Specification	− Detailed specification, tests and acceptance criteria.	v	v			
		− Compendial specification or appropriate information from the manufacturer					v
		− Specify source, including as appropriate species of animal, type of microorganism etc.		v			
	4.2. Analytical Procedures	− The analytical procedures used for testing of drug substance.	v	v			

No.	PARAMETERS	COMPONENTS	REQUIREMENTS				
			NCE	BIOTECH	MaV	MiV	G
		− Compendial methods or appropriate information from the manufacturer					v
	4.3. Validation of Analytical Procedures	- Analytical validation information, including experimental data for the analytical procedures used for testing the drug substance	v	v			
		− Non-compendial methods					v
	4.4. Batch Analyses	− Description of batches and results of the analysis to establish the specification	v	v			
	4.5. Justification of Specification	− Justification for drug substance specification.	v	v			
S5	Reference Standards or Materials	− Information on the reference standards or reference materials used for testing of the drug substance.	v	v			
		− Compendial reference standard			v*		v
S6	Container Closure System	− Descriptions of the container closure systems	v	v			
S7	Stability	− Stability report.	v	v			
		− Literature data.			v*		v
P	DRUG PRODUCT						
P1	Description and Composition	− Description − Dosage form and characteristics. − Accompanying reconstitution diluent (s) if any − Type of container and closure used for the dosage form and reconstitution diluent (s), if applicable	v	v	v*	v*	v
		Composition Name, quantity stated in metric weight or measures, function and quality standard reference.	v	v	v*	v*	v
P2	Pharmaceutical Development						
	2.1 Information on Development Studies	− Data on the development studies conducted to establish that the dosage form,	v	v			

No.	PARAMETERS	COMPONENTS	REQUIREMENTS				
			NCE	BIOTECH	MaV	MiV	G
		formulation, manufacturing process, container closure system, microbiological attributes and usage instruction are appropriate for the purpose specified in the application					
	2.2. Components of the Drug Product	− Active ingredient					
		- Justification of the compatibility of the active ingredient with excipients listed in P1 - In case of combination products, justification of the compatibility of active ingredients with each other	v	v			
		− Literature data.			v*		v
		− Excipients Justification of the choice of excipients listed in P1, which may influence the drug product performance.	v	v			
	2.3. Finished Product	− Formulation Development A brief summary describing the development of the finished product, (taking into consideration the proposed route of administration and usage for NCE and Biotech).	v	v			v
		− Overages Justification of any overage in the formulation(s) described in P1.	v	v			v
		− Physicochemical and Biological Properties Parameters relevant to the performance of the finished product e.g. pH, dissolution.	v	v			v
	2.4. Manufacturing Process Development	− Selection and optimization of the manufacturing process	v	v			
		− Differences between the manufacturing process (es) used to produce pivotal clinical batches and the process described in P.3.2, if applicable	v	v			

No.	PARAMETERS	COMPONENTS	REQUIREMENTS				
			NCE	BIOTECH	MaV	MiV	G
	2.5. Container Closure System	Suitability of the container closure system used for the storage, transportation (shipping) and use of the finished product	v	v			v
	2.6. Microbiological Attributes	Microbiological attributes of the dosage form, where appropriate	v	v	v*		v
	2.7. Compatibility	Compatibility of the finished product with reconstitution diluent(s) or dosage devices.	v	v	v*		
		Literature data					v
P3	Manufacture						
	3.1. Batch Formula	Name and quantities of all ingredients	v	v	v*		v
	3.2. Manufacturing Process and Process Control	Description of manufacturing process and process control	v	v	v*	v*	v
	3.3. Control of Critical Steps and Intermediates	Tests and acceptance criteria	v	v			v
	3.4. Process Validation and/or Evaluation	Description, documentation, and results of the validation and/or evaluation studies for critical steps or critical assays used in the manufacturing process	v	v			v
P4	Control of excipients						
	4.1. Specifications	− Specifications for excipients	v	v			
		Compendial requirements or appropriate information from the manufacturer			v*		v
	4.2. Analytical Procedures	− Analytical procedures used for testing excipients where appropriate.	v	v			
		Compendial requirements or appropriate information from the manufacturer			v*	v*	v
	4.3. Excipient of Human or Animal Origin	− Information regarding sources and or adventitious agents.	v	v			
		Compendial requirements or appropriate information from the manufacturer			v*	v*	v

No.	PARAMETERS	COMPONENTS	REQUIREMENTS				
			NCE	BIOTECH	MaV	MiV	G
	4.4. Novel Excipients	− For excipient(s) used for the first time in a finished product or by a new route of administration, full details of manufacture, characterization and controls, with cross reference to supporting safety data (non- clinical or clinical)	v	v			
P5	Control of Finished Product						
	5.1. Specification	− The specification(s) for the finished product.	v	v	v*	v*	v
	5.2. Analytical Procedures	− Analytical procedures used for testing the finished product	v	v	v*	v*	v
	5.3. Validation of Analytical Procedures	− Information including experimental data, for the analytical procedure used for testing the finished product	v	v			
		Non-compendial method	v	v	v*	v*	v
		Verification of compendial method applicability - precision & accuracy			v*	v*	v
	5.4. Batch Analyses	- Description and test results of all relevant batches	v	v			
	5.5. Characterization of Impurities	- Information on the characterization of impurities	v	v			
		- compendial requirements or appropriate information from the manufacturer			v*		v
	5.6. Justification of Specification(s)	- Justification of the proposed finished product specification(s).	v	v			
		- compendial requirements or appropriate information from the manufacturer			v*		v
P6	Reference Standards or Materials	− Information on the reference standards or reference materials used for testing of the finished product.	v	v			
		Compendial requirements or appropriate information from the manufacturer			v*		v
P7	Container Closure System	− Specification and control of primary and secondary packaging material, type of packaging and the package	v	v	v*	v*	v

No.	PARAMETERS	COMPONENTS	REQUIREMENTS				
			NCE	BIOTECH	MaV	MiV	G
		size, details of packaging inclusion (e.g. desiccant, etc.)					
P8	Stability	Stability report: data demonstrating that product is stable through its proposed shelf life. Commitment on post approval stability monitoring	V	V	V*		V
P9	Product Interchangeability						
	Equivalence evidence	− In Vitro Comparative dissolution study as required			V*		V
		− In Vivo Bioequivalence study as required			V*		V

Annex B: The Nonclinical Tabulated Summaries Template

2.1.2 Pharmacology
- 2.1.2.1 Pharmacology: Overview
- 2.1.2.2 Primary Pharmacodynamics*
- 2.1.2.3 Secondary Pharmacodynamics*
- 2.1.2.4 Safety Pharmacology
- 2.1.2.5 Pharmacodynamic Drug Interaction*

2.2.2 Pharmacokinetics
- 2.2.2.1 Pharmacokinetics: Overview
- 2.2.2.2. Analytical Methods and Validation Reports*
- 2.2.2.3 Pharmacokinetics: Absorption After a Single Dose
- 2.2.2.4 Pharmacokinetics: Absorption After Repeated Doses
- 2.2.2.5 Pharmacokinetics: Organ Distribution
- 2.2.2.6 Pharmacokinetics: Plasma Protein Binding
- 2.2.2.7 Pharmacokinetics: Study in Pregnant or Nursing Animals
- 2.2.2.8 Pharmacokinetics: Other Distribution Study
- 2.2.2.9 Pharmacokinetics: Metabolism In Vivo
- 2.2.2.10 Pharmacokinetics: Metabolism In Vitro
- 2.2.2.11 Pharmacokinetics: Possible Metabolic Pathways
- 2.2.2.12 Pharmacokinetics: Induction/Inhibition of Drug Metabolising Enzymes
- 2.2.2.13 Pharmacokinetics: Excretion
- 2.2.2.14 Pharmacokinetics: Excretion into Bile
- 2.2.2.15 Pharmacokinetics: Drug-Drug Interactions
- 2.2.2.16 Pharmacokinetics: Other

2.3.2 Toxicology
2.3.2.1 Toxicology: Overview
2.3.2.2 Toxicokinetics: Overview of Toxicokinetics Studies
2.3.2.3 Toxicokinetics: Overview of Toxicokinetics Data
2.3.2.4 Toxicology: Drug Substance
2.3.2.5 Single-Dose Toxicity
2.3.2.6 Repeat-Dose Toxicity: Nonpivotal Studies
2.3.2.7 Repeat-Dose Toxicity: Pivotal Studies
2.3.2.8 Genotoxicity: In Vitro
2.3.2.9 Genotoxicity: In Vivo
2.3.2.10 Carcinogenicity
2.3.2.11 Reproductive and Developmental Toxicity: Nonpivotal Studies
2.3.2.12 Reproductive and Developmental Toxicity: Fertility and Early Embryonic Development to Implantation (Pivotal)
2.3.2.13 Reproductive and Developmental Toxicity: Effects on Embryofoetal Development (Pivotal)
2.3.2.14 Reproductive and Developmental Toxicity: Effects on Pre- and Postnatal Development, Including Maternal Function (Pivotal)
2.3.2.15 Tolerance
2.3.2.16 Other Toxicity Studies

Annex C: Glossary

Active Pharmaceutical Ingredient (API): A substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a pharmacologically active compound. In this guideline the term '**drug substance**' is used instead of 'active pharmaceutical ingredient'.

Applicant: The person or company who submits an application for marketing authorization of a new pharmaceutical product, an update to an existing marketing authorization, or a variation to an existing marketing authorization.

Marketing Authorization Holder (MAH): A company (Applicant) in whose name the marketing authorization has been granted.

Authorized person: Is an appointed person in the manufacturing establishment with qualification, knowledge and sufficient experience who is responsible for the release of batches of finished products for sale.

Bioequivalence: Bioequivalence is defined as the lack of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutically equivalent or pharmaceutical alternative medicines become available in the general circulation or at the site of medicine action, when administered at the same molar dose, under similar conditions and in an appropriately designed study, such that their effects can be expected to be essentially the same.

Certificate of analysis: A documented testimony issued by the National Health Product Quality Control Center of Cambodia and/or other competent laboratory showing conformity or non-conformity to the specifications.

Comparator Product: A pharmaceutical product for which efficacy, safety and quality have been fully established with which a new product is intended to be interchangeable in clinical practice.

Container labelling: All information that appears on any part of a container, including that on any outer packaging.

Dosage form: The form of a therapeutic product intended for accurately and convenient delivery of active ingredient to the site of action e.g. tablet, capsule, suppository etc.

Drug substance: (=active pharmaceutical ingredient, API) A substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a pharmacologically active compound. In this guideline the term 'drug substance' is used instead of 'active pharmaceutical ingredient or API'.

Drug: see medicine / therapeutic product

Drug master file: A drug master file (DMF) is a master file that provides a full set of data on an API or an excipients or a component of a product such as a container.

Essential medicines: Essential medicines are medicinal substances identified by a given country that satisfy the health care needs of majority of population. The Essential Medicines List of Cambodia is the official policy document listing the essential medicines in Cambodia.

Evaluation report: A critical summary and interpretation and conclusions prepared by the Department of Drugs and Food, Ministry of Health, Cambodia.

Excipient: Any component of a finished dosage form other than the claimed therapeutic ingredient or ingredients.

Expert report: A report prepared by an independent expert on quality, safety and efficacy of data prepared by or on behalf of an applicant.

Finished pharmaceutical product (FPP): A medicinal product which has undergone all stages of production, including packaging in its final container and labelling, intended for marketing.

Formulation: The composition of a dosage form, including the characteristics of its raw materials and the operations required to process it.

Generic name: International non-proprietary name (INN) recommended by the World Health Organization.

Generic (Multisource) pharmaceutical product: Multisource pharmaceutical products are pharmaceutically equivalent medicines available from different and sometimes unrelated manufacturers**.**

Immediate release dosage form: A dosage form that is intended to release all the active ingredient on administration with no enhanced, delayed or extended release effect.

Innovator pharmaceutical product: A pharmaceutical product which was first authorized for marketing (normally as a patented product) on the basis of documentation of efficacy, safety and quality (according to requirements at the time of the authorization).

Interchangeable pharmaceutical product: An interchangeable pharmaceutical product is one which is therapeutically equivalent to a comparator product and can be interchanged with the comparator in clinical practice.

Intermediate product: A partly processed material which must undergo further processing before it becomes finished pharmaceutical product.

International Non-proprietary Name: A generic name, publicly owned internationally, that identifies active ingredient (s)/substance(s) of pharmaceutical product in existence worldwide.

Labelling: *see container labelling*.

License: A legal document which authorizes an individual or any entity to perform a given operation.

Manufacture (manufacturing, manufacturer): All operations of purchase of materials and products, production and packaging, quality control, release, storage, shipment of finished pharmaceutical product and related controls.

Manufacturing process validation: The documented evidence that the procedure or process operated within established parameters can perform effectively and reproducibility, based on the approved process method and product specification

Marketing authorization: An official document issued by the competent medicines regulatory authority for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy and quality. It normally contains product particulars, information on which authorization is based, approved product information` and address and name of the holder of the authorization, and the period of validity of the authorization.

Master file:

A master file is a dataset that is:

- submitted by someone other than a finished product applicant, e.g. the supplier of an active ingredient or the supplier of a packaging component;
- a common feature of more than one product, e.g. sterility test procedures; or
- some other matter that is conveniently dealt with by means of a master file.

An applicant for a new marketing authorization or for a variation may make reference to a master file, but must have the permission of the person or company that submitted the master file.

Master Formula: A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedure and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including in-process controls

Medicinal product: See pharmaceutical product

Medicine: Any preparation for human or veterinary use containing one or more active pharmaceutical ingredients, with or without pharmaceutical excipients or additives that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

New chemical entity (NCE) / New API: An active pharmaceutical substance not previously contained in any medicinal product registered in Cambodia. Those provisionally authorized at the time of the initial market inventory are not new pharmaceutical ingredients.

New medicine: Any medicine that does not match the definition of well established medicines (see below).

New pharmaceutical product: A pharmaceutical product that contains a new API, a new combination of marketed APIs, or a new multisource (generic) product.

Pharmaceutical equivalents: Products are pharmaceutical equivalents if they contain the same amount of the same active substance(s) in the same dosage form; if they meet the same or comparable standards; and if they are intended to be administered by the same route. Pharmaceutical equivalence does not necessarily imply therapeutic equivalence, as differences in the excipients and/or the manufacturing process can lead to differences in product performance.

Pharmaceutical product: Any preparation for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

Pharmacodynamic properties: Biochemical and physiological effects of medicinal products

and the mechanisms

Product information: A document defining information that may be supplied with or about a pharmaceutical product by or on behalf of the marketing authorization holder.

Provisional marketing authorization: (*synonym provisional registration*) Temporary authorization following the initial market inventory, and pending full approval based on evaluation of quality, safety and efficacy.

Quality control: Quality control is concerned with sampling, specifications and testing, and with the organization, documentation and acceptance/rejection procedures which ensure that the necessary and relevant tests are actually carried out and that starting materials, intermediates and finished products are not accepted for use, sale or supply until their quality has been judged to be satisfactory.

Register: A document maintained by the medicines regulatory authority consisting of a list of all the pharmaceutical products authorized for marketing in a Ca.

Renewal: The regular process, usually occurring every five years, by which the validity of a marketing authorization is renewed and information on a product is reviewed (validated), consolidated and sometimes expanded.

Shelf life: The period of time, in months, from the date of manufacture, that a therapeutic product is expected to remain within its approved product specification while stored under defined condition.

Specification–release: The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a pharmaceutical product at the time of its release.

Stability: The capacity of an API or dosage form to remain over a period of time within specifications established to assure its identity, purity, strength, microbiological, biopharmaceutical and physicochemical characteristics.

Stability tests: A series of tests designed to obtain information on the stability of a pharmaceutical product in order to define its shelf-life and utilisation period under specified packaging and storage conditions.

Starting material: Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials

Therapeutic equivalence: Two pharmaceutical products are considered to be therapeutically equivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and after administration in the same molar dose, their effects, with respect to both efficacy and safety, are essentially the same when administered to patients by the same route under the conditions specified in the labelling.

Tracking: Keeping a record of the progress of an application at all stages.

Transparency: The term transparency means (1) defining policies and procedures in writing and publishing the written documentation, and (2) giving reasons for decisions to the affected party. There is some overlap between transparency and accountability.

Unregistered medicinal products: Pharmaceutical products that do not have a marketing authorization.

Validation: The demonstration, with documentary evidence, that any procedure, process, equipment, material, activity, or system actually leads to the expected results.

Variation: A change to any aspect of a pharmaceutical product, including but not limited to a change to formulation, method and site of manufacture, specifications for the finished product and ingredients, container and container labelling, and product information.

WHO-type certificate: A certificate of pharmaceutical product of the type defined in the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce.