



GUIDELINE ON REGISTRATION OF MEDICINES

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NATIONAL MEDICINE REGULATORY AUTHORITY
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GUIDELINE ON GUIDELINES FOR REGISTRATION OF MEDICINES

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1. INTRODUCTION

This document “Guidelines for Registration of Medicines” will serve as the reference guide for the registration process of medicines, as defined in the NMRA Act 2015, in Sri Lanka.

This documentation shall be read in conjunction with the current laws and regulations controlling medicines in Sri Lanka. The written laws shall take precedence over this guidance document in any event of discrepancy.

The content of this Guideline shall also be read in conjunction with relevant information described in other existing World Health Organization (WHO) or International Conference on Harmonization (ICH) reference documents and guidelines.

The scope of this document includes information relating to administrative requirements and procedures for submission of an application for the registration of medicines

Applicants shall familiarize with the contents of this document and the governing legislations before they submit applications for registration of medicines.

The Authority has powers to request for information not described in this document that is deemed necessary to ensure the quality, safety, efficacy, need and price of the product.

The Authority reserves the right to amend any part of this document whenever it deems necessary. The National Medicines Regulatory Act (NMRA Act) 2015 is the main legislation that control medicines in Sri Lanka. The Authority established under NMRA Act is tasked with ensuring the quality, safety and efficacy of medicines. The NMRA reserves the right to consider the need and the price of a medicine before granting market authorization.

As per the NMRA Act, no person shall manufacture, sell, supply, import, manufacture or advertise any medicine unless the product is a registered as a medicine with the Authority.

2. ABBREVEATIONS

API	Active Pharmaceutical Ingredient
APIMF	Active Pharmaceutical Ingredient Master File
BA	Bioavailability
BE	Bioequivalence
BCS	Biopharmaceutical Classification System
BMR	Batch Manufacturing Record
BPR	Batch Packaging Record
CEP	Certificate of Suitability
cGMP	Current Good Manufacturing Practices
CPP	Certificate of Pharmaceutical Product

CTD	Common Technical Document
DOS-PD	Dossier Overall Summary of Product Dossier
EPAR	European Public Assessment Report
FDA	Food and Drug Administration
FDC	Fixed-dose Combination
FPP	Finished Pharmaceutical Product
GMP	Good Manufacturing Practices
ICH	International Conference on Harmonisation
INN	International Non-proprietary Name
JP	Japanese Pharmacopeia
OOS	Out of Specification
OSD	Oral Solid Dosage
DP	Drug Product
PAR	Public Assessment Report
PD	Product Dossier
Ph. Eur.	European Pharmacopoeia
Ph. Int.	International Pharmacopoeia
PIL	Patient Information Leaflet
PQM	Promoting the Quality of Medicines Program
PV	Process Validation
PVC	Polyvinyl Chloride
QA	Quality Assurance
QC	Quality Control
RH	Relative Humidity
DS	Drug Substance
SMPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SRA	Stringent Regulatory Authority
UDAF	Unidirectional Air Flow
UDLAF	Unidirectional Laminar Air Flow
USAID	United States Agency for International Development
USP	U. S. Pharmacopeia
WHO	World Health Organization

3. DEFINITIONS

The following definitions are provided to facilitate interpretation of the Guideline; they apply only to the words and phrases used in this Guideline.

Active pharmaceutical ingredient (API)

Any substance or combination of substances used in a finished pharmaceutical product (FPP), intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings. "Drug Substance" and "Active Substance" are synonymous to "Active Ingredient."

API starting material

A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced through in-house synthesis.

Applicant

The person or entity who submits a registration application of product to the Authority and responsible for the product information.

Batch records

All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product.

Bioavailability

The rate and relative amount of the administered drug which reaches the general circulation intact, or the rate and extent to which the API is absorbed from a drug product and becomes available at the site(s) of action.

Bioequivalence

Refer the definition given in the NMRA Act

Bio-waiver

Refer the definition given in the NMRA Act

BCS (Biopharmaceutics Classification System)

An API for which the highest dose included in the List of Essential Medicines for Sri Lanka (if the API appear in the List of Essential Medicines) or, the highest dose strength available on the market as an oral solid dosage form is soluble in 250 ml or less of aqueous media over the pH range of 1.2–6.8 at 37°C.

Clinical trial

Any systematic study on pharmaceutical products in human subjects whether in patients or non-patient volunteers in order to discover or verify the effects of, and/or identifies any adverse reaction to investigational products, and/or to study absorption, distribution, metabolism, and excretion of the products with the object of ascertaining their efficacy and safety.

Commitment batches

Production batches of an API or finished pharmaceutical product (FPP) for which the stability studies are initiated or completed post-approval through a commitment provided with the application.

Comparator product

A pharmaceutical product with which the generic product is intended to be interchangeable in clinical practice. The comparator product will normally be the innovator product for which efficacy, safety, and quality have been established.

Dosage Form

Formulation of an active ingredient(s) so that it can be administered to a patient in specified quantity/strength, e.g., tablets, capsules, injection solution, syrups, ointments, suppositories, etc. "Pharmaceutical Form" and "Finished Product" are synonymous to "Dosage Form."

Established multisource (generic) product

A multisource product that has been marketed by the applicant or manufacturer associated with the dossier for at least five years and for which at least 10 production batches were produced over the previous year, or, if less than 10 batches were produced in the previous year, not less than 25 batches were produced in the previous three years.

Excipient

Any component of a finished dosage form other than the claimed therapeutic ingredient or active ingredients.

Finished pharmaceutical product (FPP)

A finished dosage form of a pharmaceutical product that has undergone all stages of manufacture, including packaging in its final container and labeling.

Formulation

The composition of a dosage form, including the characteristics of its raw materials and the operations required to process it.

Immediate Container

That part of a product container which is in direct contact with the drug at all times.

Innovator pharmaceutical product

Generally, the pharmaceutical product that was first authorized for marketing (normally as a patented product) on the basis of documentation of efficacy, safety, and quality.

Labeling

Includes any legend, word, or mark attached to, included in, belonging to, or accompanying any drug including: 1) the immediate container label; 2) cartons, wrappers, and similar items; 3) information materials, such as instructional brochures and package inserts.

Manufacturer

A company that carries out operations such as production, packaging, repackaging, labeling, and relabeling of products.

Marketing authorization

An official document issued for the purpose of marketing or free distribution of a product after evaluation of safety, efficacy, and quality of the product.

Master formula (MF)

A document or a set of documents specifying the starting materials, with their quantities and packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including in-process controls.

Multisource (generic) pharmaceutical products

Pharmaceutically equivalent or pharmaceutical alternative products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.

Officially recognized pharmacopoeia (or compendium)

Those pharmacopoeias recognized by the Authority, i.e., The International Pharmacopoeia (Ph.Int.), European Pharmacopoeia (Ph.Eur.), British Pharmacopoeia (BP), Japanese Pharmacopoeia (JP), and the United States Pharmacopoeia (USP).

Ongoing stability study

The study carried out by the manufacturer on production batches according to a predetermined schedule in order to monitor, confirm, and extend the projected re-test period (or shelf-life) of the API, or to confirm or extend the shelf-life of the FPP.

Pharmaceutical equivalents

Products are pharmaceutically equivalent if they contain the same amount of the same active ingredient(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.

Pilot-scale batch

A batch of an API or FPP manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch; for example, for solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100,000 tablets or capsules, whichever is the larger; unless otherwise adequately justified.

Primary batch

A batch of an API or FPP used in a stability study from which stability data are submitted in a registration application for the purpose of establishing a re-test period or shelf-life.

Production batch

A batch of an API or FPP manufactured at production scale by using production equipment in a production facility as specified in the registration dossier.

Registration

- New Registration- In the registration process when the application receives at the first time and registration granted at first time
- Renewal of Registration - In the registration process some of the medicine are issued with Provisional Registrations (PR) for a defined reason. Such medicine needs to go through the process of renewal of its registration with the submission of additional documents requested.
- Re registration - Registration of a medicine is valid for 5 years. At the end of 5 years Market Authorization Holder has to apply for registration for the continuity.

Specification

A document describing in detail the requirements with which the products or materials used or obtained during manufacture have to conform. Specifications serve as a basis for quality evaluation.

Stability

The ability of an active ingredient or a drug product to retain its properties within specified limits throughout its shelf-life. The chemical, physical, microbiological, and biopharmaceutical aspects of stability must be considered.

Starting materials for synthesis

Materials that mark the beginning of the manufacturing process as described in an application or in an APIMF. A starting material for a synthetic API is a chemical compound of defined molecular structure that contributes to the structure of the API.

Validation

The demonstration, with documentary evidence, that any procedure, process, equipment, material, activity, or system actually leads to the expected results.

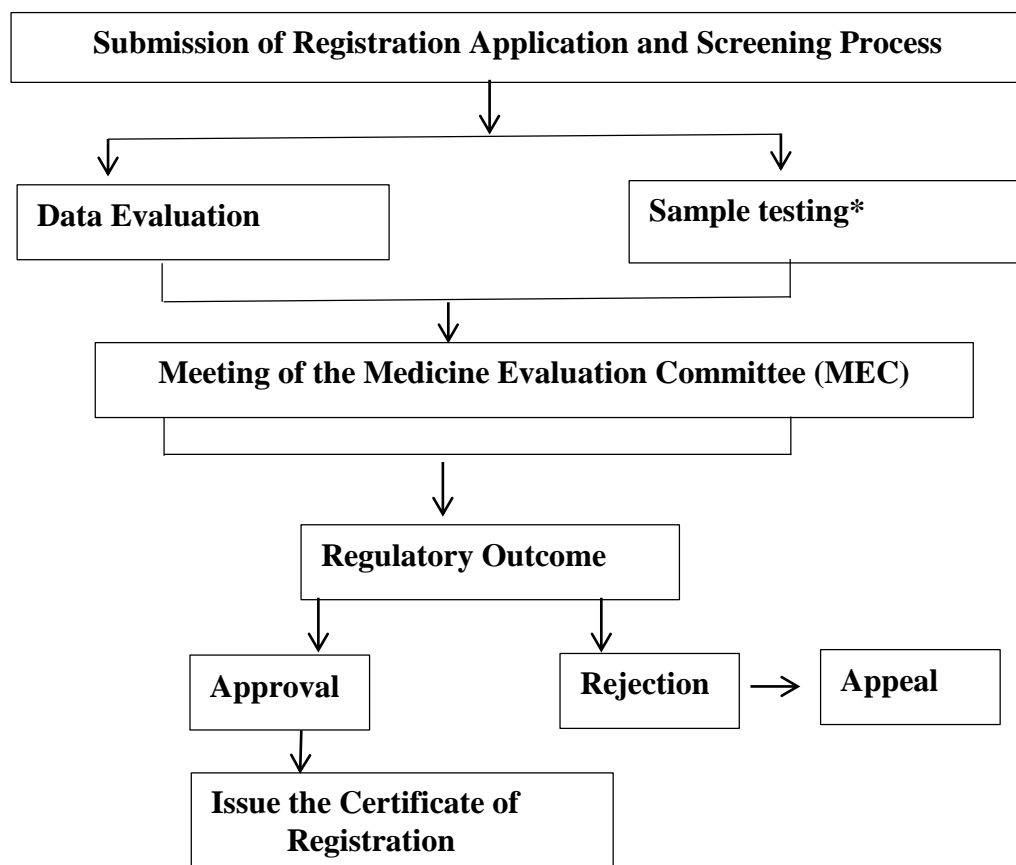
Variation

A change to any aspect of a pharmaceutical product including, but not limited to, a change to formulation, method, and site of manufacture or specifications for the finished product, ingredients, container and container labeling, and product information.

4. CATEGORIES OF APPLICATIONS FOR REGISTRATION

1. New Molecular Entities (NCE) for Sri Lanka
2. New Dosage Forms (NDF)
3. New Fixed dose Combination products
4. Biological and Biotechnological products
5. New product of existing drugs
6. Re- registration

Basic Procedure of Registration of Medicines



*for selected products

5. WHO CAN APPLY FOR REGISTRATION OF MEDICINES?

The applicant must be a locally incorporated company, corporate or legal entity, with permanent address and registered with Companies Registrar of Sri Lanka, and whose manufacturing facility has been approved for the compliance for the GMP by the NMRA.

Responsibilities of applicants

- a) To ensure that all transactions with NMRA are carried by their appointed person(s);
- b) Responsible for all information pertaining to quality, safety and efficacy in support of the product registration application; and shall inform the Authority in a timely manner any change in product information during course of evaluation;

Any person who knowingly supplies any false or misleading information to the Authority with his application for the registration of a product commits an offence.

- c) Responsible for all matters pertaining to quality, safety and efficacy of the registered product, including:

i. Data updates on product quality, safety and efficacy or Good Manufacturing Practice (GMP) compliance of the manufacturers. Any change in any document, item, sample, particulars or information which shall be notified in writing by the applicant to the Authority within fourteen 28 calendar days from the date of such change.

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

- d) To notify the Authority of any change in correspondence details, including the name, address, contact person, telephone number, fax number and email;

- e) To notify the Authority immediately upon cessation of the applicant as the product registration holder;

6. HOW TO APPLY

- Web-based online submissions via <http://www.enmra.nmra.gov.lk>

7. FEES

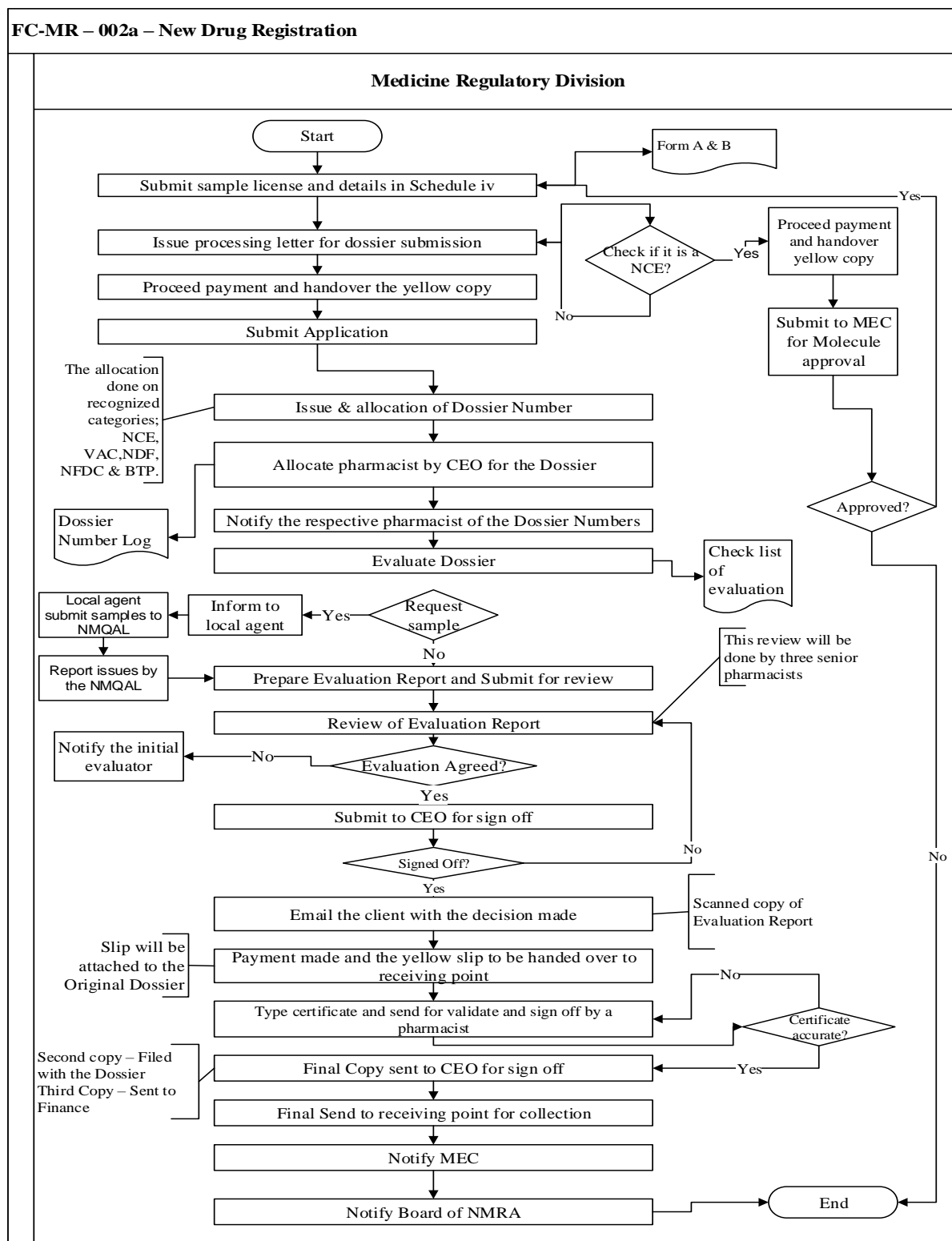
- Under the Regulation No. 2052/33, January 05, 2018 published under NMRA Act.
- The Authority may charge any applicant such costs as it may incur for the purpose of carrying out any evaluation or investigation prior to the registration of any product.
- Any payment made shall not be refundable once the application has been submitted and payment confirmed.
- Applications without the correct fees will not be processed.

8. EVALUATION AND NOTIFICATION:

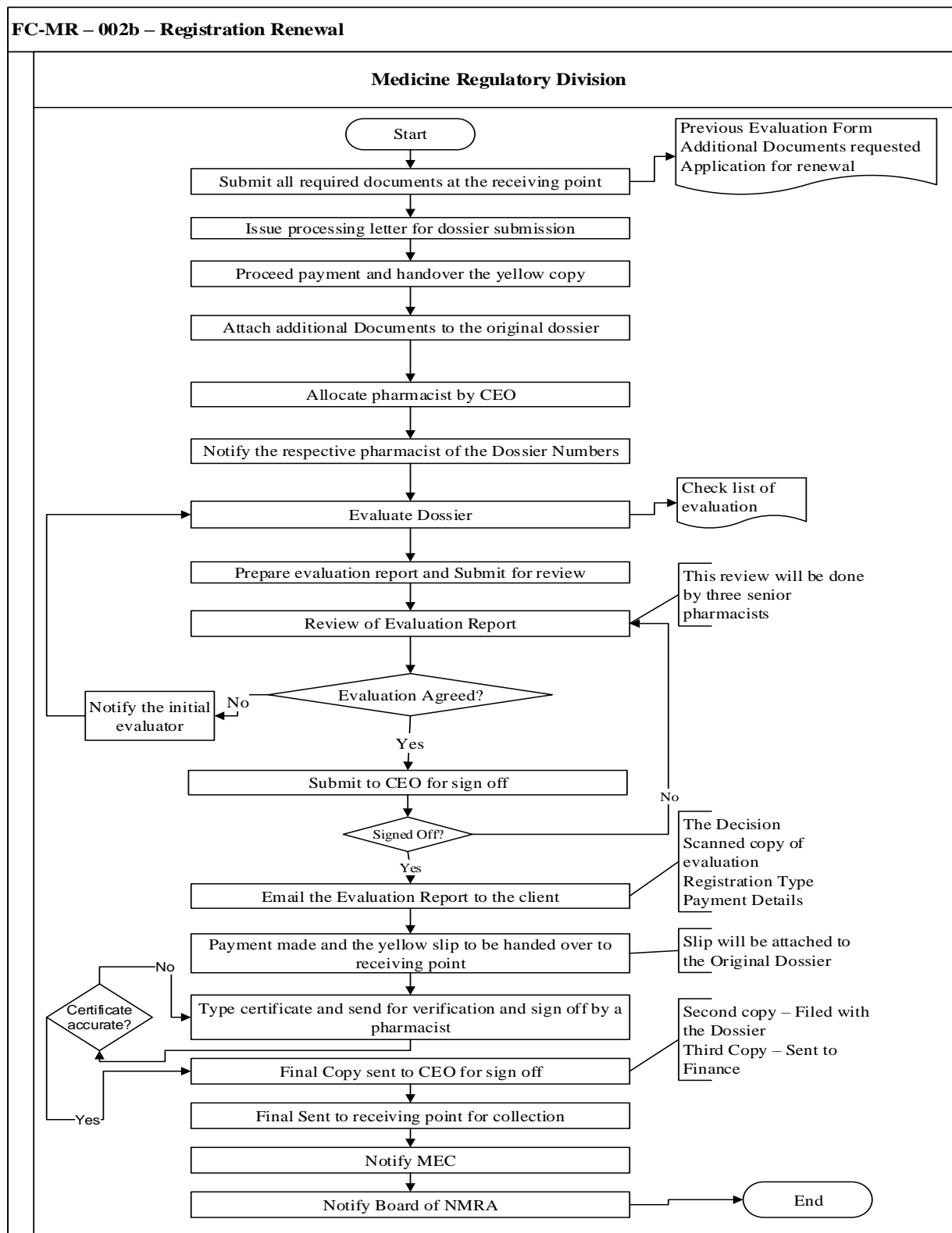
The application submitted for registration will be screened chronologically according to date of submission to the Authority, and the applicant will be notified of the results of its evaluation within 28 working days of its submission to the Authority.

9. FLOWCHARTS AND PROCEDURES

a. Submission of Dossier Procedure –New Product Registration - Flowchart

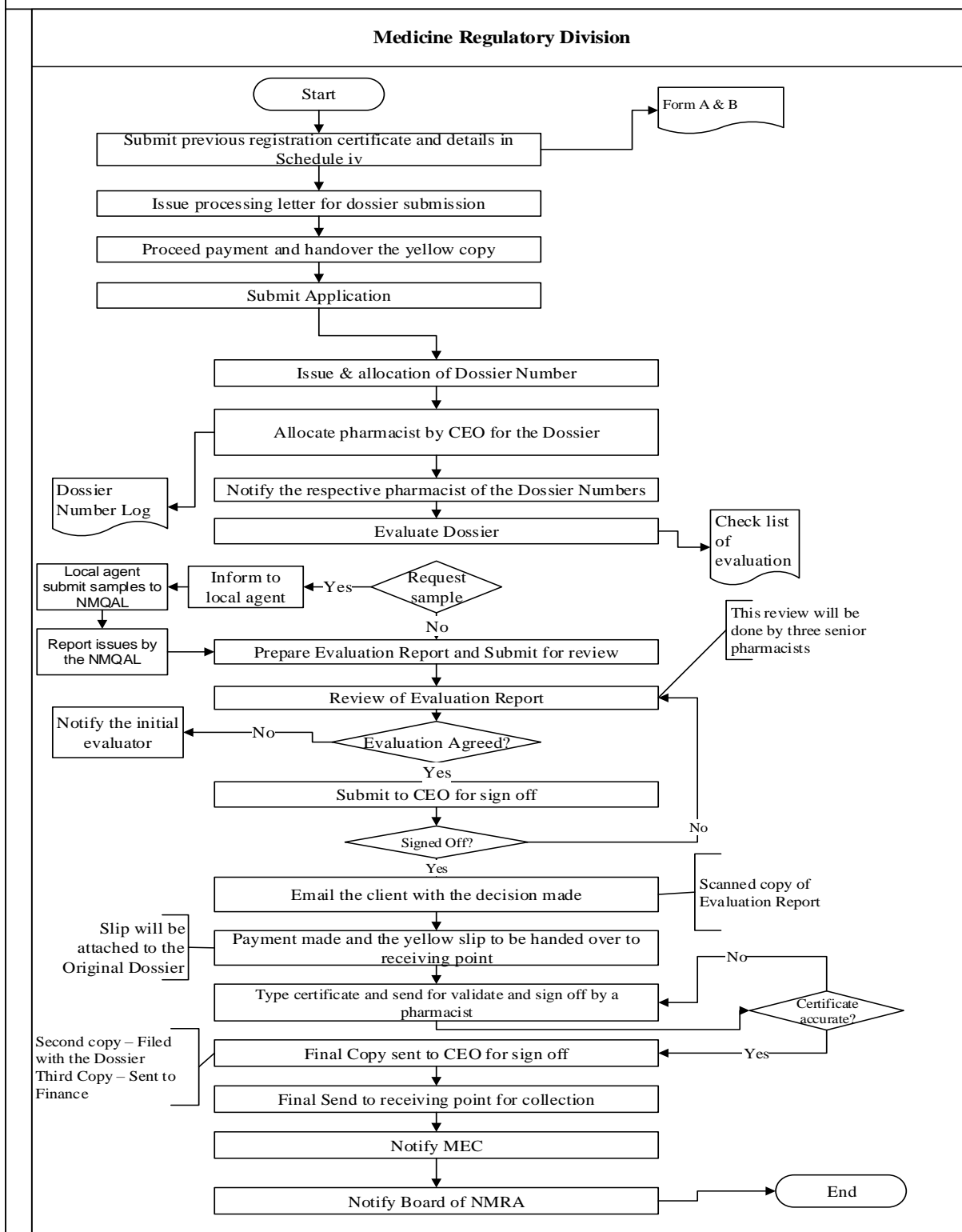


b. Registration Renewal Procedure –Flow Chart



c. Submission of Dossier Procedure – Re-Registration

FC-MR – 002c – Re- Registration Medicine



10. COMPILATION OF THE DOCUMENT

The compilation of the document should be outlined according to the respective modules and should be indexed or annotated as described in this Guideline in the Common Technical Document (CTD) format.

11. THE CTD IS ORGANIZED INTO FIVE *MODULES*;

1. **Module 1** is specific to the NMRA of Sri Lanka which includes Administrative and Product information.

Modules 2, 3, 4, and 5 are intended to be common for all situations.

2. **Module 2** – Overviews and summaries of **Modules 3–5**;
3. **Module 3** – Quality (pharmaceutical documentation);
4. **Module 4**: Non-clinical reports (pharmacology/toxicology);
5. **Module 5**: Clinical study reports

There may be a number of instances where repeated sections can be considered appropriate. Whenever a section is repeated, it should be made clear what the section refers to by creating a distinguishing heading, e.g., 3.2.S Drug substance (or API) (name, Manufacturer A).

12. THE FOLLOWING ARE GENERAL RECOMMENDATION FOR THE SUBMISSION OF THE DOSSIER:

- For generic products in which a molecule of an FPP is registered in Sri Lanka, Module 4 is not applicable;
- For an FPP where bioequivalence is not required, Module 4 and Module 5 are not applicable; and,
- For generic products in which a molecule of an FPP is registered in Sri Lanka and where a bioequivalence (BE) study is mandatory, only the BE study report should be provided in Module 5 of the dossier.

13. RECOMMENDATIONS FOR THE PRESENTATION OF THE INFORMATION IN THE MODULE 3 (*QUALITY MODULE*) FOR DIFFERENT SCENARIOS THAT MAY BE ENCOUNTERED:

- The Open part (non-proprietary information) of each APIMF should always be included in its entirety in the product dossier (PD), as an annex.
- For an FPP containing more than one API, one complete section should be provided for one API, followed by a complete, 3.2.S section for each additional API.
This may not be applicable for an API where a complete listing is not possible (e.g., multivitamin)
- For an API from multiple manufacturers one complete section should be provided for the API from one manufacturer, followed by other complete sections for an additional API manufacturer;
- For an FPP with multiple strengths (e.g., 5, 15, 20mg), a separate dossier is required for each FPP;
- For a non-sterile FPP with multiple container closure systems (e.g., bottles and unit dose blisters), one complete section should be provided with information for the different presentations provided within the subsections;

- For an sterile FPP with multiple container closure systems (Ampoule, Vials and Pre-filled syringes etc), a separate dossier is required for each FPPs;
- For different dosage forms of FPPs (e.g., tablets and capsule), a separate dossier is required for each FPP;
- For an FPP supplied with reconstitution diluents (s), one complete section should be provided for the FPP, followed by the information on the diluents (s) in a separate part as appropriate;

14. GUIDANCE FOR THE APPLICANT WITH REGARD TO COMPILATION AND FOLLOW-UP OF THE PD IS LISTED HERE:

1. The application form and the Dossier Overall Summary (DOS) of the PD should always be in electronic PDF format.
2. The attached data and documents should be in the English language.
3. Paper selection: Paper size is A4. Margins for top, bottom, header, and footer are 12.5 mm, and left and right margins are 25mm.
4. Paragraph: Single line spacing.
5. Font: Minimum type size 12point.

The weight of the font should be in such a way that it text is legible when copied.

6. Any abbreviation should be clearly defined.

15. FAST TRACK REVIEW:

Fast tract review for medicines is considered in following situations;

1. Drugs used for orphan diseases, drugs considered as “orphan” to Sri Lanka by the NMRA
2. Drugs for emergency situations shall have priority for evaluation and registration.

16. PRIORITY REVIEW:

Priority Review for medicines is considered in following situation;

1. Medicines having less than 05 products registered with the NMRA.

17. VARIATIONS

In case of requests to change the contents of specifications and test methods of the product, after reviewing of the screening application, the applicant needs to follow the “Variation Guideline” published by the NMRA.

18. BRAND (TRADE NAME):

Brand names indicating the licensed or unlicensed indications are not accepted. Brand names inappropriate for a medicine as decided by the MEC, are also not accepted.

Appoint a technical person

The local agent or the manufacturer should appoint a technical person, a pharmacist, who is able to understand regulations and related guidelines of the Authority and registration process of products, and who can communicate with the assessors in cases of need of clarification for the queries raised by the Authority that may either be product-related or administrative issues.

Module 1 – Administrative information and prescribing information

1. Cover Letter
2. Table of Contents of the Application, including Module 1 (Modules 1-5)

3. Application Form
4. Letter of Authorization by the manufacturer
5. Certificate of Pharmaceutical product
6. Certificate of Suitability (CEP), if any
7. Product Information
 - a. Summary of Product Characteristics (SPC)
 - b. Labeling Information (immediate and outer label)
 - c. Product information Leaflet (PI)
 - d. Patient Information Leaflet (PIL) where available or requested by the NMRA

Module 2 – Dossier Overall Summary of Product Dossier

1. PD Table of Contents (Modules 2-5)
2. PD Introduction
3. Quality Overall Summary of Product Dossier
4. Nonclinical Overview – generally not applicable for multisource products (some exceptions may apply)
5. Clinical Overview
6. Nonclinical Written and Tabulated Summaries – generally not applicable for multisource products (some exceptions may apply)

Module 3 – Quality

1. Table of Contents of Module 3
2. Body of Data
3. Literature References

Module 4 – Nonclinical Study Reports – generally not applicable for multisource products (some exceptions may apply)

1. Table of Contents of Module 4
2. Study Reports
3. Literature References

Module 5 – Clinical Study Reports

1. Table of Contents of Module 5
2. Tabular Listing of all Clinical Studies
3. Clinical Study Reports
4. Reports of Biopharmaceutical Studies (mainly BE study reports for generic products)
5. Case Report Forms and Individual Patient Listings – generally not applicable for multisource products (some exceptions may apply)
6. Literature References

MODULE 1: ADMINISTRATIVE AND PRODUCT INFORMATION

1.1. Covering Letter

Dated and signed letter for submission of the dossier by mentioning the product included in the dossier from the manufacturer and/or local agent responsible for registration.

1.2. Table Contents of Modules 1 to 5

Table of contents of Module 1 through Module 5 (of the PD) should be provided in Module 1.

1.3. Application Form

Completed and signed application form as provided in Annex I of this Guideline should be submitted. The date of application should correspond to the date of submission of the registration dossier to the Authority.

1.4. Agency Agreement

- I. An agency agreement should be made between the manufacturer of the product for registration and the agent responsible for the import, distribution, and sale of the product in Sri Lanka.
- II. Where the company manufactures the product at two or more places, the agreement and responsibility of each party made between the manufacturers should be submitted. In such a case, the agency agreement between the local agent and the manufacturer should be the site where the file is kept and the applicant for registration is registered.
- III. The agreement should be signed by both parties and such is what is to be presented. The seal/stamp of both parties should also be affixed to the document for agency agreement.
- IV. The appointed agent is responsible for correspondence and complete compliance with regulatory requirements pertaining to the product distribution life cycle in the country.
- V. The agreement should state that if any unsuspected and unacceptable adverse event occurs to the consumer under normal utilization, all the party's (local agent, manufacturer, and/or license holder) mentioned in the agreement will be responsible for collecting the product from the market and will be responsible for substantiating any related consequences.
- VI. The agreement should specify that both parties are responsible for pharmacovigilance and post-marketing reporting of the product safety, quality, and efficacy follow-up after marketing.

1.5. Certificate of a Pharmaceutical Product

- Certificate of a Pharmaceutical Product (CPP) issued by a competent authority in the exporting country should be provided in Module 1 in accordance with the format recommended by the W.H.O.
- The CPP should be valid at the time of submission, country specific and be the original.

1.6. Certificate of Suitability (CEP), if applicable

- A complete copy of the Certificate of Suitability (CEP), including any annexes, should be provided in *Module 1*. The declaration of access for the CEP should be duly filled out by the CEP holder on behalf of the FPP manufacturer or applicant to the Authority.
- In addition, a written commitment should be included that states the applicant will inform the Authority in the event that the CEP is withdrawn. It should also be acknowledged by the applicant

that withdrawal of the CEP will require additional consideration of the API data requirements to support the PD. The written commitment should accompany the copy of the CEP in Module 1.

- Along with the CEP, the applicant should supply the following information in the dossier, with data summarized in the PD and Module 3 of the dossier:

I. *General properties* – discussion of any additional applicable physicochemical and other relevant API properties that are not controlled by the CEP and Ph.Eur. monograph, e.g. solubility and polymorphs.

II. *Elucidation of structure and other characteristics*– studies to identify polymorphs (exception: where the CEP specifies a polymorphic form) and particle size distribution, where applicable.

III. *Specification* – the specifications of the FPP manufacturer, including all tests and limits of the CEP and Ph.Eur. monograph, and any additional tests and acceptance criteria that are not controlled in the CEP and Ph.Eur. monograph, such as polymorphs and/or particle size distribution.

IV. *Analytical procedures and validation* – for any tests in addition to those in the CEP and Ph.Eur. monograph.

V. *Batch analysis*– results from three batches of at least one pilot scale, demonstrating compliance with the FPP manufacturer’s API specifications.

VI. *Container closure system*– specifications including descriptions and identification of primary packaging components(exception: where the CEP specifies a re-test period).

1.7. Product information

- Product information including package insert (s), labeling, and summary of product characteristics (SmPC) should be provided in Module 1 of the dossier.
- All product information label statements are required to be in English. Any information appearing in the product information (labels, PIL, and SmPC) should be based on scientific justification.

1.7.1. Summary of Product Characteristics

- Recommended format for the content of the SPC is provided in Annex 3 of this Guideline.

1.7.2. Labeling (immediate and outer label)

- Only original labels or computer-ready color-printed labels (art work) are accepted for final approval.
- In the case where the text of the labels is printed directly on plastic bottles through a silk screen process, photocopies of these labels will be accepted for approval.
- The titles for batch number, manufacturing, and expiry dates should be part of the printing. If the labeling technology of the manufacturer is such that this information is to be printed on the label during production, a written commitment to show all the required information on the label of the finished product must be submitted.
- The contents of the label are given in “Guidelines for labeling” published by NMRA.

1.7.3. Product Information Leaflet (PI)

- The general content of the PIL should be prepared in line with the content of the SPC.
- Recommended format for the content of the SPC is provided in Annex 3 of this Guideline

- The contents of the PI are given in “Guidelines for labeling” published by NMRA.

1.7.4 Patient Information Leaflet (PIL)

- The general content of the PIL should be prepared in line with the content of the SPC. The PIL should not be described or presented in a manner that is false, misleading, or deceptive or is likely to create an erroneous impression regarding its use in any respect, either pictorially or in words.
- The medicines for which a PIL is a requirement and the contents of the PIL are given in “Guidelines for labeling” published by NMRA.

MODULE 2: DOSSIER OVERALL SUMMARY (DOS)

The Dossier Overall Summary (DOS) is a summary that follows the scope and the outline of the body of data provided in Module 3, Module 4 and Module 5.

- The DOS should not include information, data, or justification that was not already included in Module 3, Module 4, and Module 5 or in other parts of the dossier.
- The DOS should include sufficient information from each section to provide the assessors with an overview of the PD.
- The DOS should also emphasize critical key parameters of the product and provide, for instance, justification in cases where guidelines were not followed.
- The DOS should include a discussion of key issues that integrates information from sections in the Safety, Efficacy, and Quality Module and supporting information from other modules (e.g., qualification of impurities via toxicological studies), including cross-referencing to volume and page number in other Modules.
- The use of tables to summarize the information is encouraged, where possible. Other approaches to summarize the information can be used if they fulfil the same purpose.

MODULE 3: QUALITY

3.1. BODY OF DATA

3.1.S Drug Substance 1 (Name, Manufacturer)

3.1.S.1 General Information (Name, Manufacturer)

3.1.S.1.1 Nomenclature (name, manufacturer)

Information on the nomenclature of the drug substance should be provided. For example:

1. Recommended International Non-proprietary Name (INN);
2. Pharmacopoeia name, if relevant;
3. Chemical name(s);
4. Other non-proprietary name(s) (e.g., national name, United States Adopted Name(USAN), Japanese Accepted Name (JAN), British Approved Name (BAN)) and Chemical Abstracts Service (CAS) registry number.

*A **CAS Registry Number**, also referred to as CASRN or **CAS Number**, is a unique numerical identifier assigned by the **Chemical Abstracts Service (CAS)** to every **chemical** substance described in the open scientific literature.*

5. Anatomical Therapeutic Chemical (ATC) Class

*The Anatomical Therapeutic Chemical (ATC) Classification System is a drug classification system that classifies the **active** ingredients of drugs according to the organ or system on which they act and their therapeutic, **pharmacological** and chemical properties.*

The listed chemical names should be consistent with those appearing in scientific literature and those appearing on the product labeling information (e.g., summary of product characteristics; package leaflet, also known as patient information leaflet or PIL; or labeling). Where several names exist, the INN name should be indicated.

3.1.S.1.2 Structure (name, manufacturer)

- The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided.
- For bio-tech drug substance, the schematic amino acid sequence indicating glycosylation sites or other post-translational modifications and relative molecular mass should be provided, as appropriate.

3.1.S.1.3 General properties (name, manufacturer)

- A list should be provided of physicochemical and other relevant properties of the drug substance, including biological activity for Biotech. (Reference: ICH Guidelines Q6A and Q6B). This information can be used in developing the specifications, in formulating FPPs, and in testing for release and stability purposes.
- The physical and chemical properties of the API should be discussed, including the physical description, solubility in common solvents (e.g., water, alcohols, dichloromethane, acetone), quantitative aqueous pH solubility profile (e.g., pH 1.2 to 6.8, dose/solubility volume), polymorphism, pH and pKa values, UV absorption maxima and molar absorptivity, melting point, refractive index (for a liquid), hygroscopicity, partition coefficient, etc. This list is not intended to be exhaustive, but provides an indication as to the type of information that could be included.

3.1. S.2 Manufacture (Name, Manufacturer)

3.1. S.2.1 Manufacturer(s) (name, manufacturer)

- The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.
- The list of manufacturers/companies should specify the actual addresses of production or manufacturing site(s) involved (including block(s) and units(s)), rather than the administrative offices. Telephone number(s), fax number(s) and e-mail address(es) should be provided.
- A valid manufacturing authorization should be provided for the production of APIs. If available, a certificate of GMP compliance should be provided in the PD in Module 1.

3.1.S.2.2 Description of manufacturing process and process controls (name, manufacturer)

- The description of the drug substance manufacturing process represents the applicant's commitment for the manufacture of the drug substance. Information should be provided to adequately describe the manufacturing process and process controls.
- For a synthetic drug substance, a flow diagram of the synthetic process(es) should be provided that includes molecular formulae, weights, yield ranges, chemical structures of starting materials,

intermediates, reagents and API reflecting stereochemistry, and identifies operating conditions and solvents.

- Where possible, and for confidentiality reasons, the holder of the APIMF can submit the restricted part of the APIMF to the Authority. In this case, if detailed information is presented in the restricted part, the information to be provided for this section of the applicant FPP PD includes a flow chart (including molecular structures and all reagents and solvents) and a brief outline of the manufacturing process, with special emphasis on the final steps, including purification procedures.
- For sterile APIs, full validation data on the sterilization process should be provided in the Open part (in cases where there is no further sterilization of the final product).
- For biotech drug substance, information should be provided on the manufacturing process, which typically starts with a vial(s) of the cell bank, and includes cell culture, harvest(s), purification and modification reactions, filling, storage, and shipping conditions. An explanation of the batch numbering system, including information regarding any pooling of harvests or intermediates and batch size or scale should be provided.
- A flow diagram should be provided that illustrates the manufacturing route from the original inoculum (e.g., cells contained in one or more vials(s) of the Working Cell Bank up to the last harvesting operation. The diagram should include all steps (i.e., unit operations) and intermediates. Relevant information for each stage, such as population doubling levels, cell concentration, volumes, pH, cultivation times, holding times, and temperature, should be included. Critical steps and critical intermediates for which specifications are established (as mentioned in 3.1.S.2.4) should be identified.
- A description of each process step in the flow diagram should be provided. Information should be included on, for example, scale; culture media and other additives (details provided in 3.1.S.2.3); major equipment (details provided in 3.1.A.1); and process controls, including in-process tests and operational parameters, process steps, equipment and intermediates with acceptance criteria (details provided in 3.1.S.2.4).
- Where polymorphic/amorphous forms have been identified, the form resulting from the synthesis should be stated. Where particle size is considered a critical attribute, the particle size reduction method(s) (milling, micronization) should be described.
- Where there are multiple manufacturing sites for one API manufacturer, a comprehensive list, in tabular form, should be provided comparing the processes at each site and highlighting any differences.

3.1. S.2.3 Control of materials (name, manufacturer)

- Materials 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.
- The carry-over of impurities of the starting materials for synthesis into the final API should be considered and discussed.

- A letter of attestation should be provided confirming that the API and the starting materials and reagents used to manufacture the API are *without* risk of transmitting agents of animal spongiform encephalopathies. When available, a CEP demonstrating Transmissible Spongiform Encephalopathy (TSE)-compliance should be provided. A complete copy of the CEP (including any annexes) should be provided in Module 1.

3.1. S.2.4 Controls of critical steps and intermediates (name, manufacturer)

Critical Steps:

- Tests and acceptance criteria (with justification including experimental data) performed at critical steps identified in 3.1.S.2.2 of the manufacturing process to ensure that the process is controlled should be provided.

Intermediates:

- Information on the quality and control of intermediates isolated during the process should be provided. Specifications for isolated intermediates should be provided and should include tests and acceptance criteria for identity, purity and assay, where applicable

Additionally for Biotech: Stability data supporting storage conditions should be provided. (Reference: ICH Guideline Q5C)

3.1. S.2.5 Process validation and/or evaluation (name, manufacturer)

- It is expected that the manufacturing processes for all APIs are properly controlled. If the API is prepared as sterile, a complete description should be provided for aseptic processing and/or sterilization methods. The controls used to maintain the sterility of the API during storage and transportation should also be provided.
- For biotech drug substances, sufficient information should be provided on validation and evaluation studies to demonstrate that the manufacturing process (including reprocessing steps) is suitable for its intended purpose and to substantiate selection of critical process controls (operational parameters and in-process tests) and their limits for critical manufacturing steps (e.g., cell culture, harvesting, purification, and modification).
- The plan for conducting the study should be described and the results, analysis and conclusions from the executed study should be provided. The analytical procedures and corresponding validation should be cross-referenced (e.g., 3.1.S.2.4, 3.1.S.4.3) or provided as part of justifying the selection of critical process controls and acceptance criteria.
- For manufacturing steps intended to remove or inactivate viral contaminants, the information from evaluation studies should be provided in 3.1.A.2.

3.1.S.2.6 Manufacturing process development (name, manufacturer)

- A description and discussion should be provided of the significant changes made to the manufacturing process and/or manufacturing site of the API used in producing comparative bioavailability or bio-waiver, scale-up, pilot, clinical and, if available, production scale batches.
- Testing used to assess the impact of manufacturing changes on the drug substance(s) and the corresponding drug product(s) can also include nonclinical and clinical studies. Cross-reference to the location of these studies in other modules of the submission should be included

3.1.S.3 Characterization (Name, Manufacturer)

3.1.S.3.1 Elucidation of structure and other characteristics (name, manufacturer)

- Confirmation of structure based on, e.g., synthetic route and spectral analyses should be provided. Information such as the potential for isomerism, the identification of stereochemistry, or the potential for forming polymorphs should also be included.
- For biotech drug substance for the desired product and product-related substances, details should be provided on primary, secondary, and higher-order structure, post-translational forms (e.g., glycoforms), biological activity, purity, and immunochemical properties, when relevant. [Reference: ICH Guideline Q6B]

Elucidation of structure

- The PD should include quality assurance (QA)-certified copies of the spectra, peak assignments, and a detailed interpretation of the data of the studies performed to elucidate and/or confirm the structure of the API. The DOS-PD should include a list of the studies performed and a conclusion from the studies that the results support the proposed structure.
- For APIs that are not described in an officially recognized pharmacopoeia, the studies carried out to elucidate and/or confirm the chemical structure normally include elemental analysis, infrared (IR), ultraviolet (UV), nuclear magnetic resonance (NMR), and mass spectra (MS) studies. Other tests could include X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC).
- For APIs that are described in an officially recognized pharmacopoeia, it is generally sufficient to provide copies of the IR spectrum of the API from each of the proposed manufacturer(s) runs concomitantly with a pharmacopoeial reference standard. See Section 3.1.S.5 for details on acceptable reference standards or materials.

Isomerism/stereochemistry

- When an API is chiral, it should be specified whether specific stereoisomers or a mixture of stereoisomers have been used in the clinical or the comparative bio-studies, and information should be given as to the stereoisomer of the API that is to be used in the FPP.

Polymorphism

- Many APIs can exist in different physical forms in the solid state. Polymorphism is characterized as the ability of an API to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice. Amorphous solids consist of disordered arrangements of molecules and do not possess a distinguishable crystal lattice. Solvates are crystal forms containing either stoichiometric or nonstoichiometric amounts of a solvent. If the incorporated solvent is water, the solvates are also commonly known as hydrates.
- Polymorphic forms of the same chemical compound differ in internal solid-state structure and, therefore, may possess different chemical and physical properties, including packing, thermodynamic, spectroscopic, kinetic, interfacial, and mechanical properties. These properties can have a direct impact on API process-ability, pharmaceutical product manufacturability, and product quality/performance, including stability, dissolution and bioavailability. Unexpected appearance or disappearance of a polymorphic form may lead to serious pharmaceutical consequences.

3.1.S.3.2 Impurities (name, manufacturer)

- Information on impurities should be provided. [Reference: ICH Guidelines Q3A, Q3C, Q5C, Q6A, and Q6B]
- Regardless of whether a pharmacopoeial standard is claimed, a discussion should be provided of the potential and actual impurities arising from the synthesis, manufacture, or degradation of the API. This should cover starting materials, by-products, intermediates, chiral impurities, and degradation products and should include the chemical names, structures, and origins. The discussion of pharmacopoeial APIs should not be limited to the impurities specified in the API monograph.

Identification threshold

- It is recognized by the pharmacopoeias that APIs can be obtained from various sources and thus can contain impurities not considered during the development of the monograph. Furthermore, a change in the production or source may give rise to additional impurities that are not adequately controlled by the official pharmacopoeia monograph. As a result, each PD is assessed independently to consider the potential impurities that may arise from the proposed route(s) of synthesis. For these reasons, the ICH limits for unspecified
 - impurities (e.g., NMT 0.10% or 1.0 mg per day intake (whichever is lower) for APIs having a maximum daily dose of ≤ 2 g/day) are generally recommended, rather than the general limits for unspecified impurities that may appear in the official pharmacopoeia monograph that could potentially be higher than the applicable ICH limit.

Qualification of impurities

- The ICH impurity guidelines should be consulted for options on the qualification of impurities. The limit specified for an identified impurity in an *officially recognized pharmacopoeia* is generally considered to be qualified. The following is an additional option for qualification of impurities in existing APIs:
 - The limit for an impurity present in an existing API can be accepted by comparing the impurity results found in the existing API with those observed in an innovator product using the same validated, stability-indicating analytical procedure (e.g., comparative high performance liquid chromatography (HPLC) studies). If samples of the innovator product are not available, the impurity profile may also be compared to a different comparator (market leading) FPP with the same route of administration and similar characteristics (e.g., tablet versus capsule). It is recommended that the studies be conducted on comparable samples (e.g., age of samples) to obtain a meaningful comparison of the impurity profiles.
 - Levels of impurities generated from studies under accelerated or stressed storage conditions of the innovator or comparator FPP are not considered acceptable/qualified.
 - A specified impurity present in the existing API is considered qualified if the amount of the impurity in the existing API reflects the levels observed in the innovator or comparator (market leading) FPP.
 - ICH class II solvent(s) used prior to the last step of the manufacturing process may be exempted from routine control in API specifications if suitable justification is provided. Submission of results demonstrating less than 10% of the ICH Q3C limit (option I) of the solvent(s) in three consecutive production-scale batches or six consecutive pilot-scale batches of the API or a suitable intermediate would be considered acceptable justification. The last-step solvents used in the process should always be routinely controlled in the final API. The limit for residues of triethylamine (TEA) is either 320 ppm on the basis of ICH Q3C (option 1) or 3.2 mg/day on the basis of permitted daily exposure (PDE).

- The absence of known, established, highly toxic impurities (genotoxic) used in the process or formed as a by-product should be discussed and suitable limits should be proposed. The limits should be justified by appropriate reference to available guidance's (e.g., EMEA/CHMP/QWP/251344/2006 or USFDA Guidance for Industry: Genotoxic and carcinogenic impurities in drug substances and products, recommended approaches,
- Residues of metal catalysts used in the manufacturing process and determined to be present in batches of API are to be controlled in specifications. This requirement does not apply to metals that are deliberate components of the pharmaceutical substance (such as a counter ion of a salt) or metals that are used as a pharmaceutical excipient in the FPP (e.g., an iron oxide pigment). The guideline on the specification limits for residues of metal catalysts or metal reagents, EMEA/CHMP/SWP/4446/2000, or any equivalent approaches can be used to address this issue. The requirement normally does not apply to extraneous metal contaminants that are more appropriately addressed by GMP, WHO Good Distribution Practices for Pharmaceutical Products (GDP), or any other relevant quality provision such as the heavy metal test in monographs of recognized pharmacopoeias that cover metal contamination originating from manufacturing equipment and the environment.

3.1.S.4 Control of Drug Substance (name, manufacturer)

3.1.S.4.1 Specification (name, manufacturer)

- The specification for the drug substance should be provided. Copies of the API specifications, dated and signed by authorized personnel (e.g., the person in charge of the quality control or quality assurance department) should be provided in the PD, including specifications from each API manufacturer as well as those of the FPP manufacturer.
- The FPP manufacturer's API specification should be summarized according to the table in the DOS-PD template under the headings tests, acceptance criteria, and analytical procedures (including types, sources, and versions for the methods).
- The *standard* declared by the applicant could be an officially recognized pharmacopoeia standard (e.g., Ph.Int., Ph.Eur., BP, USP, JP) or a House (manufacturer's) standard.
- The *specification reference number and version* (e.g., revision number and/or date) should be provided for version control purposes.
- For the analytical procedures, the *type* should indicate the kind of analytical procedure used (e.g., visual, IR, UV, HPLC, laser diffraction); the *source* refers to the origin of the analytical procedure (e.g., Ph.Int., Ph.Eur., BP, USP, JP, in-house); and the *version* (e.g., code number/version/date) should be provided for version control purposes.
- In cases where there is more than one API manufacturer, the FPP manufacturer's API specifications should be one single compiled set of specifications that is identical for each manufacturer. It is acceptable to lay down in the specification more than one acceptance criterion and/or analytical method for a single parameter with the statement —for API from manufacturer A (e.g., in the case of residual solvents).
- Any non-routine testing should be clearly identified as such and justified along with the proposal on the frequency of non-routine testing.
- The ICH Q6A guideline outlines recommendations for a number of *universal* and *specific tests* and criteria for APIs. [Reference: ICH Guidelines Q3A, Q3C, Q6A; officially recognized pharmacopoeia]

3.1.S.4.2 Analytical procedures (name, manufacturer)

- The analytical procedures used for testing the drug substance should be provided. Copies of the in-house analytical procedures used to generate testing results provided in the PD, as well as those proposed for routine testing of the API by the FPP manufacturer should be provided. Unless modified, it is not necessary to provide copies of officially recognized pharmacopoeia analytical procedures.
- The system suitability tests (SSTs) represent an integral part of the method and are used to ensure the adequate performance of the chosen chromatographic system. As a minimum, HPLC and GC purity methods should include SSTs for resolution and repeatability. For HPLC methods to control API-related impurities, this is typically done using a solution of the API with a concentration corresponding to the limit for unspecified impurities. Resolution of the two closest eluting peaks is generally recommended. However, the choice of alternate peaks can be used if justified (e.g., choice of a toxic impurity). The method for repeatability test should include an acceptable number of replicate injections. HPLC assay methods should include SSTs for repeatability and in addition either peak asymmetry, theoretical plates or resolution. For thin layer chromatography (TLC) methods, the SSTs should verify the ability of the system to separate and detect the analyte(s) (e.g., by applying a spot corresponding to the API at a concentration corresponding to the limit of unspecified impurities). [Reference: ICH Guideline Q2; WHO Technical Report Series, No. 943, Annex 3]

3.1.S.4.3 Validation of analytical procedures (name, manufacturer)

- Analytical validation information, including experimental data for the analytical procedures used for testing the drug substance, should be provided.
- Copies of the validation reports for the analytical procedures used to generate testing results, as well as those proposed for routine testing of the API by the FPP manufacturer should be provided.
- In general, verification is not necessary for pharmacopoeia API *assay* methods. However, specificity of a specific pharmacopoeia assay method should be demonstrated if there are any potential impurities that are not specified in the pharmacopoeia monograph. If an officially recognized pharmacopoeia method is used to control API-related impurities that are not specified in the monograph, full validation of the method is expected with respect to those impurities.
- If an officially recognized pharmacopoeia standard is claimed and an in-house method is used in lieu of the pharmacopoeia method (e.g., for assay or for specified impurities), equivalency of the in-house and pharmacopoeia methods should be demonstrated. This could be accomplished by performing duplicate analyses of one sample by both methods and providing the results from the study. For impurity methods, the sample analyzed should be the API spiked with impurities at concentrations equivalent to their specification limits.

3.1.S.4.4 Batch analyses (name, manufacturer)

- Description of batches and results of batch analyses should be provided. The information provided should include batch number, batch size, date and production site of relevant API batches used in comparative bioavailability or biowaiver studies, preclinical and clinical data (if relevant), stability, pilot, scale-up and, if available, production-scale batches. This data is used to establish the specifications and evaluate consistency in API quality.

- Analytical results should be provided from at least two batches of, at least, pilot-scale from each proposed manufacturing site of the API and should include the batch(es) used in the comparative bioavailability or biowaiver studies. A pilot-scale batch should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.
- Copies of the certificates of analysis, both from the API manufacturer(s) and the FPP manufacturer, should be provided for the profiled batches and any company responsible for generating the test results should be identified. The FPP manufacturer's test results should be summarized in the DOS-PD.
- The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as —all tests meet specifications. For quantitative tests (e.g., individual and total impurity tests and assay tests), it should be ensured that actual *numerical results* are provided rather than vague statements such as —within limits or —conforms.
- A discussion and justification should be provided for any incomplete analyses (e.g., results not tested according to the proposed specification).

3.1.S.4.5 Justification of specification (name, manufacturer)

- Justification for the drug substance specification should be provided.
- A discussion should be provided on the inclusion of certain tests, evolution of tests, analytical procedures and acceptance criteria, differences from the officially recognized pharmacopoeia standard(s), etc. If the officially recognized pharmacopoeia methods have been modified or replaced, a discussion should be included.
- The justification for certain tests, analytical procedures and acceptance criteria may have been discussed in other sections of the PD (e.g., impurities, particle size distribution) and does not need to be repeated here, although a cross-reference to their location should be provided. [Reference: ICH Guidelines Q3A, Q3C, Q6A; *officially recognized pharmacopoeia*]

3.1.S.5 Reference Standards or Materials (Name, Manufacturer)

- Information should be provided on the reference standard(s) used to generate data in the PD, as well as those to be used by the FPP manufacturer in routine API and FPP testing.
- The source(s) of the reference standards or materials used in the testing of the API should be provided (e.g., those used for the identification, purity, assay tests). These could be classified as *primary* or *secondary* reference standards.
- A secondary (or in-house) reference standard can be used by establishing it against a suitable primary reference standard, e.g., by providing legible copies of the IR of the primary and secondary reference standards run concomitantly and by providing its certificate of analysis, including assay determined against the primary reference standard. [Reference: ICH Guideline Q6A; WHO Technical Report Series, No. 943, Annex 3]

3.1.S.6 Container Closure System (Name, Manufacturer)

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

- Copies of the labels applied on the secondary packaging of the API should be provided and should include the conditions of storage. In addition, the name and address of the manufacturer of the API should be stated on the container, regardless of whether relabeling is conducted at any stage during the API distribution process.

3.1.S.7 Stability (Name, Manufacturer)

3.1.S.7.1 Stability summary and conclusions (name, manufacturer)

- 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 re-test date or shelf-life, as appropriate.

Stress testing

- As outlined in the ICH Q1A guidance document, stress testing of the API can help identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual API and the type of FPP involved.
- Stress testing may be carried out on a single batch of the API. For examples of typical stress conditions, refer to WHO Technical Report Series, No. 953, Annex 2, Section 2.1.2, as well as, —A typical set of studies of the degradation paths of an active pharmaceutical ingredient, in WHO Technical Report Series, No. 929, Annex 5, Table A.1.
- When available, it is acceptable to provide the relevant data published in the scientific literature (inter alia WHOPARs, EPARs) to support the identified degradation products and pathways.

Accelerated and long-term testing

- Available information on the stability of the API under accelerated and long-term conditions should be provided, including information in the public domain or obtained from scientific literature. The source of the information should be identified.
- The preferred long-term storage conditions for APIs is either 30°C±2°C/65%±5%RH or 30°C±2°C/75%±5%RH. Alternative conditions should be supported with appropriate evidence, which may include literature references or in-house studies, demonstrating that storage at 30°C is inappropriate for the API. For APIs intended for storage in a refrigerator and those intended for storage in a freezer refer to the stability guideline, WHO Technical Report Series, No. 953 Annex 2. APIs intended for storage below -20°C should be treated on a case-by-case basis.
- To establish the re-test period, data should be provided on not less than three batches of, at least, pilot-scale. The batches should be manufactured by the same synthesis route as production batches and using a method of manufacture and procedure that simulates the final process to be used for production batches. The stability testing program and results should be summarized in the dossier and in the tables in the PD.
- The information on the stability studies should include details such as storage conditions, batch number, batch size, container closure system, and completed (and proposed) test intervals. The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as all tests meet specifications.

- Ranges of analytical results where relevant and any trends that were observed should be included. For quantitative tests (e.g., individual and total degradation product tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements, such as “within limits” or “conforms”.
- Where different from the methods described in S.4.2, descriptions and validation of the methodology used in stability studies should be provided.
- The data required at the time of submitting the dossier (in general) are:

Storage temperature (°C)	Relative humidity (%)	Minimum time period (months)
Accelerated 40±2	75±5	6
Intermediate *	*	*
Long-term 30±2	75±5	6

Ongoing stability studies

- The stability of the API should be monitored according to a continuous and appropriate program that will permit the detection of any stability issue (e.g., changes in levels of degradation products). The purpose of the ongoing stability program is to monitor the API and to determine that the API remains and can be expected to remain within the re-test period in all future batches.
- At least one production batch per year of API (unless none is produced during that year) should be added to the stability monitoring program and tested at least annually to confirm the stability. In certain situations, additional batches should be included. A written commitment (signed and dated) from API manufacturer for ongoing stability studies should be included in the dossier.
- Refer to WHO Technical Report Series, No. 953, Annex 2, Section 2.1.11, for further information on ongoing stability studies.

3.1.S.7.3 Stability data (name, manufacturer)

- The actual stability results used to support the proposed re-test period should be included in the dossier. The result should be presented in an appropriate format such as tabular, graphical, or narrative description. Information on the analytical procedures used to generate the data and validation of these procedures should be included. For quantitative tests (e.g., individual and total degradation product tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements such as “within limits” or “conforms.” [Reference: ICH Guidelines Q1A, Q1B, Q1D, Q1E, Q2; WHO Technical Report Series, No. 953, Annex 2]

3.2. P Drug Product (Finished Pharmaceutical Product (FPP))

3.1.P.1 Description and Composition of the FPP (Name, Dosage Form)

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

Description of the dosage form

- The description of the FPP should include the physical description, available strengths, release mechanism (e.g., immediate, modified (delayed or extended)), as well as any other distinguishable characteristics.

Composition of the dosage form

- Composition of the dosage form, and their amounts on a per unit basis (including overages, if any), the function of the components, and a reference to their quality standards (e.g., pharmacopoeia monographs or manufacturer's specifications) should be provided.
- All components used in the manufacturing process should be included, including those that may not be added to every batch (e.g., acid and alkali), those that may be removed during processing (e.g., solvents), and any others (e.g., nitrogen, silicon for stoppers).
- If the FPP is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated (e.g., 1 mg of active ingredient base = 1.075 mg active ingredient hydrochloride).
- All overages should be clearly indicated (e.g., contains 2% overage of the API to compensate for manufacturing losses).
- The components should be declared by their proper or common names, quality standards (e.g., Ph.Int., Ph.Eur., BP, USP, JP, House) and, if applicable, their grades (e.g., Microcrystalline Cellulose NF (PH 102)) and special technical characteristics (e.g., lyophilized, micronized, solubilized, emulsified).
- The function of each component (e.g., diluent/filler, binder, disintegrant, lubricant, glidant, granulating solvent, coating agent, antimicrobial preservative) should be stated. If an excipient performs multiple functions, the predominant function should be indicated.
- The qualitative composition, including solvents, should be provided for all proprietary components or blends (e.g., capsule shells, coloring blends, imprinting inks). This information (excluding the solvents) is to be listed in the product information (e.g., summary of product characteristics, labeling, and package leaflet).

Description of accompanying reconstitution diluent(s)

- For FPPs supplied with reconstitution diluent(s) that are commercially available or have been assessed and considered acceptable in connection with another PD with the Authority, a brief description of the reconstitution diluents(s) should be provided.

Type of container and closure

- The container closure used for the FPP (and accompanying reconstitution diluent, if applicable) should be briefly described, with further details provided under 3.1.P.7

3.1.P.2 Pharmaceutical Development (Name, Dosage Form)

- The Pharmaceutical Development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes, and usage instructions are appropriate for the purpose specified in the product dossier.

3.1.P.2.1 Components of the FPP (name, dosage form)

3.1.P.2.1.1 Active pharmaceutical ingredient (name, dosage form)

- The compatibility of the API with excipients listed in 3.1.P.1 should be discussed.

3.1.P.2.1.2 Excipients (name, dosage form)

- When choosing excipients including colouring agents, those with a pharmacopoeia monograph are generally preferred. Other resources are available for information on acceptable excipients and their concentrations, such as the FDA IIG list and the *Handbook of Pharmaceutical Excipients*.

- Use of excipients in concentrations outside of established ranges are discouraged and generally requires justification.
- Where relevant, compatibility study results (e.g., compatibility of a primary or secondary amine API with lactose) should be included to justify the choice of excipients. Specific details should be provided where necessary (e.g., use of potato or corn starch).
- Where preservatives and antioxidants are included in the formulation, the effectiveness of the proposed concentration of the antioxidant as well as its safety should be justified and verified by appropriate studies.

3.1.P.2.2.1 Formulation development (name, dosage form)

- A brief summary describing the development of the FPP should be provided, taking into consideration the proposed route of administration and usage. The differences between the comparative bioavailability or biowaiver formulations and the formulation (i.e., composition) described in 3.1.P.1 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 requirements for bioequivalence studies should be taken into consideration, for example, when formulating multiple strengths and/or when the product(s) may be eligible for a biowaiver. Product clinical information, including bioequivalence and biowaiver justification, should be documented under Module 5.
- If the proposed FPP is a functionally scored tablet, a study should be undertaken to ensure the uniformity of dose in the tablet fragments.

In vitro dissolution or drug release

- A discussion should be included as to how the development of the formulation relates to development of the dissolution method(s) and the generation of the dissolution profile whereas the finished product quality specifications are in-house.
- Recommendations for conducting and assessing comparative dissolution profiles can be found in *WHO Technical Report Series*, No. 863 - Thirty-fourth Report and *WHO Technical Report Series*, No. 937, 2006.

3.1.P.2.2.2 Overages (name, dosage form)

- Any overages in the formulation(s) described in 3.1.P.1 should be justified.
- Justification of an overage to compensate for loss during manufacture should be provided, including the step(s) where the loss occurs, the reasons for the loss, and batch analysis release data (assay results).
- Overages for the sole purpose of extending the shelf-life of the FPP are generally not acceptable.

3.1.P.2.3 Manufacturing process development (name, dosage form)

The selection and optimization of the manufacturing process described in 3.1.P.3.3, in particular its critical aspects, should be explained. Where relevant, justification for the selection of aseptic processing or other sterilization methods over terminal sterilization should be provided.

3.1.P.2.4 Container closure system (name, dosage form)

- The suitability of the container closure system (described in 3.1.P.7) used for the storage, transportation (shipping), and use of the FPP should be discussed. 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 construction, and performance (such as reproducibility of the dose delivery from the device when presented as part of the FPP).

- For a device accompanying a multi-dose container, the results of a study should be provided demonstrating the reproducibility of the device (e.g., consistent delivery of the intended volume), generally at the lowest intended dose.
- A sample of the device should be provided in Module 1.

3.1.P.2.5 Microbiological attributes (name, dosage form)

- Where appropriate, the microbiological attributes of the dosage form should be discussed, including, for example, the rationale for not performing microbial limits testing for non-sterile products and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed.
- Where an antimicrobial preservative is included in the formulation, the amount used should be justified by submission of results of the product formulated with different concentrations of the preservative(s) to demonstrate the least necessary but still effective concentration. The effectiveness of the agent should be justified and verified by appropriate studies (e.g., USP or Ph.Eur. general chapters on antimicrobial preservatives) using a batch of the FPP.
- If the lower bound limit for the proposed acceptance criterion for the assay of the preservative is less than 90.0%, the effectiveness of the agent should be established with a batch of the FPP containing a concentration of the antimicrobial preservative corresponding to the lower proposed acceptance criteria.

3.1.P.2.6 Compatibility (name, dosage form)

- The compatibility of the FPP with reconstitution diluent(s) or dosage devices (e.g., precipitation of API in solution, sorption on injection vessels, stability) should be addressed to provide appropriate and supportive information for the labeling.
- Where a device is required for oral liquids or solids (e.g., solutions, emulsions, suspensions and powders/granules for such reconstitution) that are intended to be administered immediately after being added to the device, the compatibility studies mentioned in this Guideline are not required.
- Where sterile, reconstituted products are to be further diluted, compatibility should be demonstrated with all diluents over the range of dilution proposed in the labeling. These studies should preferably be conducted on aged samples. Where the labeling does not specify the type of containers, compatibility (with respect to parameters such as appearance, pH, assay, levels of individual and total degradation products, sub visible particulate matter, and extractables from the packaging components) should be demonstrated in glass, PVC, and polyolefin containers. However, if one or more containers are identified in the labeling, compatibility of admixtures needs to be demonstrated only in the specified containers.
- Studies should cover the duration of storage reported in the labeling (e.g., 24 hours under controlled room temperature and 72 hours under refrigeration).

3.1.P.3 Manufacture (name, dosage form)

3.1.P.3.1 Manufacturer(s) (name, dosage form)

- The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.
- The facilities involved in the manufacturing, packaging, labeling and testing should be listed. If certain companies are responsible only for specific steps (e.g., manufacturing of an intermediate) such should be clearly indicated in the dossier.
- The list of manufacturers/companies should specify the *actual addresses* of production or manufacturing site(s) involved (including block(s) and unit(s)), rather than the administrative offices.
- For a mixture of an API with an excipient, the blending of the API with the excipient is considered to be the critical step in the manufacture of the final product and therefore the mixture does not fall under the definition of an API. The only exceptions are in the cases where the API cannot exist on its own. Similarly, for a mixture of APIs, the blending of the APIs is considered to be the critical step in the manufacture of the final product. Sites for such manufacturing steps should be included in this section.
- For each site where the major production step(s) are carried out, when applicable, attach a WHO-type certificate of product issued by a competent authority in terms of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (Module 1).
- When there are differences between the product for which this application is submitted and that marketed in the country/countries which provided the WHO-type certificate(s), provide data to support the applicability of the certificate(s) despite the differences. Depending on the case, it may be necessary to provide validation data for differences in site of manufacture, specifications, formulation, etc. Note that only minor differences are likely to be acceptable.

3.1.P.3.2 Batch formula (name, dosage form)

- A batch formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages, and a reference to their quality standards.
- The tables in the PD template should be used to summarize the batch formula of the FPP *for each proposed commercial batch size* and express the quantity of each component on a per batch basis, including a statement of the total weight or measure of the batch.
- All components used in the manufacturing process should be included, including those that may not be added to every batch (e.g., acid and alkali), those that may be removed during processing (e.g., solvents) and any others (e.g., nitrogen, silicon for stoppers). If the FPP is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated (e.g., 1 kg of active ingredient base = 1.075 kg active ingredient hydrochloride). All overages should be clearly indicated (e.g., Contains 5 kg (corresponding to 2%) overage of the API to compensate for manufacturing losses).
- The components should be declared by their proper or common names, quality standards (e.g., Ph.Int., Ph.Eur., BP, USP, JP, House) and, if applicable, their grades (e.g., Microcrystalline Cellulose NF (PH 102)) and special technical characteristics (e.g., lyophilized, micronized, solubilized, emulsified).

3.1.P.3.3 Description of manufacturing process and process controls (name, dosage form)

- 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.
- A narrative description of the manufacturing process, including packaging that represents the sequence of steps undertaken and the scale of production should also be provided. Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater level of detail. Equipment should, at least, be identified by type (e.g., tumble blender, in-line homogenizer) and working capacity, where relevant.
- Steps in the process should have the appropriate process parameters identified, such as time, temperature, or pH associated numeric values can be presented as an expected range. Numeric ranges for critical steps should be justified in Section 3.1.P.3.4. In certain cases, environmental conditions (e.g., low humidity for an effervescent product) should be stated.
- The maximum holding time for bulk FPP prior to final packaging should be stated. The holding time should be supported by the submission of stability data, if longer than 30 days. For an aseptically processed sterile product, the holding of the filtered product and sterilized component prior to filling should be under UD-LAF (Class A) system and filling should be done immediately within 24hrs.
- Proposals for the reprocessing of materials should be justified. Any data to support this justification should be either referenced to development section or filed in this section
- The information above should be summarized in the DOS-PD template and should reflect the production of the proposed commercial batches. For the manufacture of sterile products, the class (e.g., class A, B, C, etc.) of the areas should be stated for each activity (e.g., compounding, filling, sealing, etc.), as well as the sterilization parameters for equipment, container/closure, terminal sterilization etc.

3.1.P.3.4 Controls of critical steps and intermediates (name, dosage form)

- **Critical Steps:** Tests and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps identified in 3.1.P.3.3 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.
- Examples of applicable in-process controls include:
 - a) granulations: moisture (limits expressed as a range), blend uniformity (e.g., low dose tablets), bulk and tapped densities, particle size distribution;
 - b) solid oral products: average weight, weight variation, hardness, thickness, friability, and disintegration checked periodically throughout compression, weight gain during coating;
 - c) semi-solids: viscosity, homogeneity, pH;
 - d) transdermal dosage forms: assay of API-adhesive mixture, weight per area of coated patch without backing;
 - e) metered dose inhalers: fill weight/volume, leak testing, valve delivery;
 - f) dry powder inhalers: assay of API-excipient blend, moisture, weight variation of individually contained doses such as capsules or blisters;
 - g) liquids: pH, specific gravity, clarity of solutions; and,
 - h) parenterals: appearance, clarity, fill volume/weight, pH, filter integrity tests, particulate matter, leak testing of ampoules.

[Reference: ICH Guidelines Q2, Q6A, Q8, Q9, Q10; WHO Technical Report Series, No. 929, Annex 5]

3.1.P.3.5 Process validation and/or evaluation (name, dosage form)

- Description, documentation, and results of the validation and/or evaluation studies should be provided for critical steps or critical assays used in the manufacturing process (e.g., validation of the sterilization process or aseptic processing or filling). Viral safety evaluation should be provided in 3.1A.2, if necessary.
- For products that meet the criteria of an *established multisource product*, a product quality review as outlined in Appendix 1 may be submitted in lieu of the information below.
- The following information should be provided for all other products:
 - a copy of the *process validation protocol*, specific to this FPP, that identifies the critical equipment and process parameters that can affect the quality of the FPP and defines testing parameters, sampling plans, analytical procedures and acceptance criteria;
 - a *commitment* that three consecutive, production-scale batches of this FPP will be subjected to *prospective validation* in accordance with the above protocol. The applicant should submit a written commitment that information from these studies will be available for verification after registration by the Authority inspection team; and,
 - if the process validation studies have already been conducted (e.g., for sterile products), a copy of the *process validation report* should be provided in the PD in lieu of (a) and (b) above.
- One of the most practical forms of process validation, mainly for non-sterile products, is the final testing of the product to an extent greater than that required in routine quality control. It may involve extensive sampling, far beyond that called for in routine quality control and testing to normal quality control specifications and often for certain parameters only. Thus, for instance, several hundred tablets per batch may be weighed to determine unit dose uniformity. The results are then treated statistically to verify the "normality" of the distribution and to determine the standard deviation from the average weight. Confidence limits for individual results and for batch homogeneity are also estimated. Strong assurance is provided that samples taken at random will meet regulatory requirements if the confidence limits are well within pharmacopoeia specifications.
- Similarly, extensive sampling and testing may be performed with regard to any quality requirements. In addition, intermediate stages may be validated in the same way, e.g., dozens of samples may be assayed individually to validate mixing or granulation stages of low-dose tablet production by using the content uniformity test. Products (intermediate or final) may occasionally be tested for non-routine characteristics. Thus, sub visual particulate matter in parenteral preparations may be determined by means of electronic devices, or tablets/capsules tested for dissolution profile, if such tests are not performed on every batch.
- Where ranges of batch sizes are proposed, it should be shown that variations in batch size would not adversely alter the characteristics of the finished product. It is envisaged that those parameters listed in the following validation scheme will need to be re-validated once further scale-up is proposed after registration.
- The process validation protocol should include inter alia the following:
 - a reference to the current master production document;
 - a discussion of the critical equipment;

- the process parameters that can affect the quality of the FPP (critical process parameters (CPPs)), including challenge experiments and failure mode operation;
 - details of the sampling—sampling points, stages of sampling, methods of sampling, and the sampling plans (including schematics of blender/storage bins for uniformity testing of the final blend);
 - the testing parameters/acceptance criteria including in-process and release specifications and including comparative dissolution profiles of validation batches against the batch(es) used in the bioavailability or biowaiver studies;
 - the analytical procedures or a reference to appropriate section(s) of the dossier;
 - the methods for recording/evaluating results; and,
 - the proposed timeframe for completion of the protocol.
- The manufacture of sterile FPPs needs a well-controlled manufacturing area (e.g., a strictly controlled environment, highly reliable procedures, and appropriate in-process controls). A detailed description of these conditions, procedures and controls should be provided, together with actual copies of the following standard operating procedures:
- washing, treatment, sterilizing, and depyrogenating of containers, closures, and equipment;
 - filtration of solutions;
 - lyophilization process;
 - leaker test of filled and sealed ampoules;
 - final inspection of the product;
 - sterilization cycle; and,
 - routine environmental monitoring and media fill validation exercise.
- The sterilization process used to destroy or remove microorganisms is probably the single most important process in the manufacture of parenteral FPPs. The process can make use of moist heat (e.g., steam), dry heat, filtration, gaseous sterilization (e.g., ethylene oxide), or radiation. It should be noted that terminal steam sterilization, when practical, is considered to be the method of choice to ensure sterility of the final FPP. Therefore, scientific justification for selecting any other method of sterilization should be provided.
- The sterilization process should be described in detail and evidence should be provided to confirm that it will produce a sterile product with a high degree of reliability and that the physical and chemical properties as well as the safety of the FPP will not be affected. Details, such as Fo range, temperature range, and peak dwell time for an FPP and the container closure should be provided. Although standard autoclaving cycles of 121°C for 15 minutes or more would not need a detailed rationale; such justifications should be provided for reduced temperature cycles or elevated temperature cycles with shortened exposure times. If ethylene oxide is used, studies and acceptance criteria should control the levels of residual ethylene oxide and related compounds.
- Filters used should be validated with respect to pore size, compatibility with the product, absence of extractable, and adsorption of the API or any of the components.
 - For the validation of aseptic filling of parenteral products that cannot be terminally sterilized, simulation process trials should be conducted. This involves filling ampoules with culture media under normal conditions, followed by incubation and control of microbial growth. A level of contamination of less than 0.1% is considered to be acceptable.[Reference: ICH Guidelines Q8, Q9, Q10; WHO Technical Report Series, Nos. 902 and 908]

3.1.P.4 Control of Excipients (Name, Dosage Form)

3.1.P.4.1 Specifications (name, dosage form)

- The specifications from the applicant or the FPP manufacturer should be provided for all excipients, including those that may not be added to every batch (e.g., acid and alkali), those that do not appear in the final FPP (e.g., solvents) and any others used in the manufacturing process (e.g., nitrogen, silicon for stoppers).
- If the standard claimed for an excipient is an officially recognized pharmacopoeia standard, it is sufficient to state that the excipient is tested according to the requirements of that standard, rather than reproducing the specifications found in the officially recognized pharmacopoeia monograph.
- If the standard claimed for an excipient is a non-pharmacopoeia standard (e.g., House standard) or includes tests that are supplementary to those appearing in the officially recognized pharmacopoeia monograph, a copy of the specification for the excipient should be provided.
- For excipients of natural origin, microbial limit testing should be included in the specifications. Skip testing is acceptable, if justified (submission of acceptable results of five production batches).
- For oils of plant origin (e.g., soy bean oil, peanut oil), the absence of aflatoxins or biocides should be demonstrated.
- The colors permitted for use are limited to those listed in the —Japanese pharmaceutical excipients, the EU —List of permitted food colors, and the US FDA —Inactive ingredient guide. For proprietary mixtures, the supplier's product sheet with the qualitative formulation should be submitted, in addition to the FPP manufacturer's specifications for the product, including identification testing.
- For flavors, the qualitative composition should be submitted, as well as a declaration that the excipients comply with foodstuff regulations (e.g., US FDA or EU).
- Information that is considered confidential may be submitted directly to the Authority by the supplier with reference to the specific related product.
- Other certifications of at-risk components may be required on a case-by-case basis.
- If additional purification is undertaken on commercially available excipients, details of the process of purification and modified specifications should be submitted.

3.1.P.4.2 Analytical procedures (name, dosage form)

- The analytical procedures used for testing the excipients should be provided, where appropriate.
- Copies of analytical procedures from officially recognized pharmacopoeia monographs do not need to be submitted.

3.1.P.4.3 Validation of analytical procedures (name, dosage form)

- Copies of analytical validation information are generally not submitted for the testing of excipients, with the exception of the validation of in-house methods where appropriate.

3.1.P.4.4 Justification of specifications (name, dosage form)

- A discussion of the tests that are supplementary to those appearing in the officially recognized pharmacopoeia monograph should be provided.

3.1.P.4.5 Excipients of human or animal origin (name, dosage form)

- 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). For more detail, see Section 3.1.A.2.
- The following excipients should be addressed in this section: gelatin, phosphates, stearic acid, magnesium stearate and other stearates. If from plant origin a declaration to this effect will suffice.
- For these excipients from animal origin, a letter of attestation should be provided confirming that the excipients used to manufacture the FPP are *without* risk of transmitting agents of animal spongiform encephalopathies.
- Materials of animal origin should be avoided whenever possible.

3.1.P.4.6 Novel excipients (name, dosage form)

- For excipient(s) used for the first time in an FPP or by a new route of administration, full details of manufacture, characterization, and controls, with cross references to supporting safety data (nonclinical and/or clinical) should be provided according to the API and/or FPP intended purpose. (Details should be provided in 3.1.A.3).

3.1.P.5 Control of FPP (name, dosage form)

3.1.P.5.1 Specification(s) (name, dosage form)

- A copy of the FPP specification(s) from the applicant (as well as the company responsible for the batch release of the FPP, if different from the applicant), dated and signed by authorized personnel (i.e., the person in charge of the quality control or quality assurance department) should be provided in the PD.
- The specifications should be summarized according to the tables in the PD template including the tests, acceptance criteria and analytical procedures (including types, sources and versions for the methods):
 - the *standard* declared by the applicant could be an officially recognized pharmacopoeia standard (e.g., Ph.Int., BP, USP, JP) or a House (manufacturer's) standard;
 - the *specification reference number and version* (e.g., *revision number and/or date*) should be provided for version control purposes; and,
 - for the analytical procedures, the *type* should indicate the kind of analytical procedure used (e.g., visual, IR, UV, HPLC), the *source* refers to the origin of the analytical procedure (e.g., Ph.Int., Ph.Eur., BP, USP, JP, in-house), and the *version* (e.g., *code number/version/date*) should be provided for version control purposes.
- Specifications should include, at minimum, tests for appearance, identification, assay, purity, pharmaceutical tests (e.g., dissolution), physical tests (e.g., loss on drying, hardness, friability, particle size, apparent density), uniformity of dosage units, identification of coloring materials, identification and assay of antimicrobial or chemical preservatives (e.g., antioxidants), and microbial limit tests.
- The following information provides guidance for specific tests:
 - a) fixed-dose combination FPPs (FDC-FPPs):

- analytical methods that can distinguish each API in the presence of the other API(s) should be developed and validated,
 - acceptance criteria for degradation products should be established with reference to the API they are derived from. If an impurity results from a chemical reaction between two or more APIs, its acceptance limits should be calculated with reference to the worst case (the API with the smaller area under the curve). Alternatively the content of such impurities could be calculated in relation to their reference standards,
 - when any one API is present at less than 25 mg or less than 25% of the weight of the dosage unit, a test and limit for content uniformity is required for each API in the FPP,
 - when all APIs are present at equal or greater than 25 mg and equal or greater than 25% of the weight of the dosage unit, a test and limit for weight variation may be established for the FPP, in lieu of content uniformity testing;
 - modified-release products: a meaningful API release method;
 - b) inhalation and nasal products:
 - consistency of delivered dose (throughout the use of the product), particle or droplet size distribution profiles (comparable to the product used in in-vivo studies, where applicable) and if applicable for the dosage form, moisture content, leak rate, microbial limits, preservative assay, sterility and weight loss;
 - c) suppositories: uniformity of dosage units, melting point;
 - d) transdermal dosage forms: peel or shear force, mean weight per unit area, dissolution; and,
 - e) sterile: sterility, endotoxin.
- Unless there is appropriate justification, the acceptable limit for the API content of the FPP in the release specifications is $\pm 5\%$ of the label claim (i.e., 95.0-105.0%).
 - Skip testing is acceptable for parameters such as identification of coloring materials and microbial limits, when justified by the submission of acceptable supportive results for five production batches. When skip testing justification has been accepted, the specifications should include a footnote, stating at minimum the following skip testing requirements: at minimum, every tenth batch and at least one batch annually is tested. In addition, for stability-indicating parameters such as microbial limits, testing will be performed at release and shelf-life during stability studies.
 - Any differences between release and shelf-life tests and acceptance criteria should be clearly indicated and justified. Note that such differences for parameters, such as dissolution and moisture content, are normally not accepted.[Reference: ICH Guidelines Q3B, Q3C, Q6A; official monograph]

3.1.P.5.2 Analytical procedures (name, dosage form)

- Copies of the in-house analytical procedures used during pharmaceutical development (if used to generate testing results provided in the PD) as well as those proposed for routine testing should be provided. Unless modified, it is not necessary to provide copies of officially recognized pharmacopoeia analytical procedures.
- Tables for summarizing a number of the different analytical procedures and validation information (e.g., HPLC assay/impurity methods) can be found in the 2.3.R Regional information section of the QOS-PD (i.e., 2.3.R.2). These tables should be used to summarize the analytical procedures used for determination of the assay, related substances and dissolution of the FPP.
- Refer to Section 3.1.S.4.2 of this Guideline for additional guidance on analytical procedures.

3.1.P.5.3 Validation of analytical procedures (name, dosage form)

- Copies of the validation reports for the in-house analytical procedures used during pharmaceutical development (if used to support testing results provided in the PD) as well as those proposed for routine testing should be provided.
- Tables for summarizing a number of the different analytical procedures and validation information (e.g., HPLC assay/impurity methods, GC methods) can be found in the 2.3.R Regional information section of the QOS-PD (i.e., 2.3.R.2). These tables should be used to summarize the validation information of the analytical procedures used for determination of the assay, related substances, and dissolution of the FPP.
- As recognized by regulatory authorities and pharmacopoeias themselves, verification of pharmacopoeia methods can be necessary. The pharmacopoeia methods, as published, are typically validated based on an API or an FPP originating from a specific manufacturer. Different sources of the same API or FPP can contain impurities and/or degradation products or excipients that were not considered during the development of the monograph. Therefore, the monograph and pharmacopoeia method(s) should be demonstrated suitable for the control of the proposed FPP.
- For officially recognized pharmacopoeia FPP *assay* methods, verification should include a demonstration of specificity, accuracy, and repeatability (method precision). If an officially recognized pharmacopoeia method is used to control related substances that are not specified in the monograph, full validation of the method is expected with respect to those related substances.
- If an officially recognized pharmacopoeia standard is claimed and an in-house method is used in lieu of the pharmacopoeia method (e.g., for assay or for related compounds), equivalency of the in-house and pharmacopoeia methods should be demonstrated. This could be accomplished by performing duplicate analyses of one sample by both methods and providing the results from the study. For related compound methods, the sample analyzed should be the placebo spiked with related compounds at concentrations equivalent to their specification limits.

3.1.P.5.4 Batch analyses (name, dosage form)

- Information should include strength and batch number, batch size, date and site of production and use (e.g., used in comparative bioavailability or biowaiver studies, preclinical and clinical studies (if relevant), stability, pilot, scale-up and, if available, production-scale batches) on relevant FPP batches used to establish the specification(s) and evaluate consistency in manufacturing.
- Analytical results tested by the company responsible for the batch release of the FPP (generally, the applicant or the FPP manufacturer, if different from the applicant) should be provided for not less than two batches of commercial scale
- The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as —all tests meet specifications. This should include ranges of analytical results, where relevant. For quantitative tests (e.g., individual and total impurity tests and assay tests), it should be ensured that actual *numerical results* are provided rather than vague statements such as —within limits or —conforms (e.g., —levels of degradation product A ranged from 0.2 to 0.4 %). Dissolution results should be expressed at minimum as both the average and range of individual results.
- A discussion and justification should be provided for any incomplete analyses (e.g., results not tested according to the proposed specification). [Reference: ICH Guidelines Q3B, Q3C, Q6A; official monograph]

3.1.P.5.5 Characterization of impurities (name, dosage form)

- A discussion should be provided of all impurities that are potential degradation products (including those among the impurities identified in 3.1.S.3.2 as well as potential degradation products resulting from interaction of the API with other APIs (FDCs), excipients, or the container closure system) and FPP process-related impurities (e.g., residual solvents in the manufacturing process for the FPP). [Reference: ICH Guidelines Q3B, Q3C, Q6A]

3.1.P.5.6 Justification of specification(s) (name, dosage form)

- A discussion should be provided on the omission or inclusion of certain tests, evolution of tests, analytical procedures and acceptance criteria, differences from the officially recognized pharmacopoeia standard(s), etc. If the officially recognized pharmacopoeia methods have been modified or replaced, a discussion should be included.
- The justification for certain tests, analytical procedures, and acceptance criteria (e.g., degradation products, dissolution method development) may have been discussed in other sections of the PD and does not need to be repeated here, although a cross-reference to its location should be provided.
- ICH Guideline Q6A should be consulted for the development of specifications for FPPs.

3.1.P.6 Reference standards or materials (name, dosage form)

- Information on the reference standards or reference materials used for testing of the FPP should be provided, if not previously provided in —3.1.S.5 Reference Standards or Materials.
- See Section 3.1.S.5 for information that should be provided on reference standards or materials. Information should be provided on reference materials of FPP degradation products, where not included in 3.1.S.5.[Reference: ICH Guideline Q6A; WHO Technical Report Series, No. 943, Annex 3]

3.1.P.7 Container Closure System (name, dosage form)

- A description of the container closure systems should be provided, including the identity of materials of construction of each primary packaging component and its specification. The specifications should include description and identification (and critical dimensions, with drawings where appropriate). Non-pharmacopoeia methods (with validation) should be included, where appropriate.
- For non-functional secondary packaging components (e.g., those that neither 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 3.1.P.2.
- The WHO *Guidelines on packaging for pharmaceutical products* (WHO Technical Report Series, No. 902, Annex 9, 2002) and the officially recognized pharmacopoeias should be consulted for recommendations on the packaging information for FPPs.
- Descriptions, materials of construction and specifications (of the company responsible for packaging the FPP, generally the FPP manufacturer) should be provided for the packaging components that are:
 - in direct contact with the dosage form (e.g., container, closure, liner, desiccant, filler);

- used for drug delivery (including the device(s) for multi-dose solutions, emulsions, suspensions, and powders/granules for such);
 - used as a protective barrier to help ensure stability or sterility; and,
 - necessary to ensure FPP quality during storage and shipping.
- The specifications for the primary packaging components should include a specific test for identification (e.g., IR). Specifications for film and foil materials should include limits for thickness or area weight.
 - Information to establish the suitability (e.g., qualification) of the container closure system should be discussed in Section 3.1.P.2.

3.1.P.8 Stability (Name, Dosage Form)

3.1.P.8.1 Stability summary and conclusions (name, dosage form)

- The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include, for example, conclusions with respect to storage conditions and shelf-life, and, if applicable, in-use storage conditions and shelf-life.

Stress testing

- Photostability testing should be conducted on at least one primary batch of the FPP, if appropriate. If “protect from light” is stated in one of the officially recognized pharmacopoeias for the API or FPP, it is sufficient to state “protect from light” on labeling, in lieu of photostability studies, when the container closure system is shown to be light protective. Additional stress testing of specific types of dosage forms may be appropriate (e.g., cyclic studies for semi-solid products, freeze-thaw studies for liquid products).

Accelerated, intermediate (if necessary) and long-term testing

- Stability data must demonstrate stability of the medicinal product throughout its intended shelf-life under the climatic conditions of Sri Lanka. Refer to WHO Technical Report Series, No. 953, Annex 2, Appendix 1, for information on climatic zones. According to Annex 2, Appendix 1, the required long-term storage conditions for Sri Lanka is $30^{\circ}\text{C}\pm 2^{\circ}\text{C}/75\%\pm 5\%\text{RH}$. The minimum long-term storage condition should thus fulfill the storage conditions $30^{\circ}\text{C}\pm 2^{\circ}\text{C}/75\%\pm 5\%\text{RH}$, as recommended by WHO, can also be acceptable. The use of alternative long-term conditions will need to be justified and should be supported with appropriate evidence.
- Other storage conditions are outlined in the WHO stability guideline for FPPs packaged in impermeable and semi-permeable containers and those intended for storage in a refrigerator and in a freezer. FPPs intended for storage below -20°C should be treated on a case-by-case basis.
- The minimum data required at the time of submission of the dossier (in general):

Storage temperature (°C)	Relative humidity (%)	Minimum time period (months)
Accelerated 40 ± 2	75 ± 5	6
Long-term 30 ± 2	65 ± 5 or 75 ± 5	To cover the complete shelf-life

The information on the stability studies should include details such as

- a) storage conditions;
- b) strength;

- c) batch number, including the API batch number(s) and manufacturer(s);
- d) batch size;
- e) container closure system, including orientation (e.g., erect, inverted, on-side), where applicable;
- and,
- f) completed test intervals.

- The discussion of test results should focus on observations noted for the various tests, rather than reporting comments such as —all tests meet specifications. This should include ranges of analytical results and any trends that were observed. For quantitative tests (e.g., individual and total degradation product tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements such as —within limits or —conforms. Dissolution results should be expressed at minimum as both the average and range of individual results.
- Applicants should consult the ICH Q1E guidance document for details on the evaluation and extrapolation of results from stability data (e.g., if significant change was not observed within six months at accelerated condition and the data show little or no variability, the proposed shelf-life could be up to two times the period covered by the long-term data, but should not exceed the long-term data by 12 months).

Proposed storage statement and shelf-life

- The proposed storage statement and shelf-life (and in-use storage conditions and in-use period, if applicable) for the FPP should be provided.[Reference: WHO TRS No. 953, Annex 2; ICH Guidelines Q1A, Q1B, Q1C, Q1D, Q1E, Q3B, Q6A]

3.1.P.8.2 Post-approval stability protocol and stability commitment (name, dosage form)

Primary stability study commitment

- When available long-term stability data on primary batches do not cover the proposed shelf-life granted at the time of assessment of the PD, a commitment should be made to continue the stability studies in order to firmly establish the shelf-life.
- A written commitment (signed and dated) to continue long-term testing over the shelf-life period should be included in the dossier.

Commitment stability studies

- The long-term stability studies for the *commitment batches* should be conducted through the proposed shelf-life on at least three production batches of each strength in each container closure system. Where stability data was not provided for three production batches of each strength, a written commitment (signed and dated) should be included in the dossier.

Ongoing stability studies

- An *ongoing stability program* is established to monitor the product over its shelf-life and to determine that the product remains and can be expected to remain within specifications under the storage conditions on the label. Unless otherwise justified, at least one batch per year of product manufactured in every strength and in every container closure system, if relevant, should be included in the stability program (unless none is produced during that year).
- Bracketing and matrixing may be applicable. A written commitment (signed and dated) to this effect should be included in the dossier.
- Any differences in the stability protocols used for the primary batches and those proposed for the *commitment batches* or *ongoing batches* should be scientifically justified.

3.1.P.8.3 Stability data (name, dosage form)

- 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 indicated.
- The actual stability results/reports used to support the proposed shelf-life should be provided in the PD. For quantitative tests (e.g., individual and total degradation product tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements such as —within limits‖ or —conforms.‖ Dissolution results should be expressed, at minimum, as both the average and range of individual results.

3.1.A Appendices

3.1.A.1 Facilities and Equipment

Not applicable except for biotech products.

3.1.A.2 Adventitious Agents Safety Evaluation

Provide details of any viral safety evaluation of blood biotech products.

3.1.A.3 Novel Excipients

Provide details of safety (refer to Module 4) and clinical documentation (refer to Module 5) for excipients used for the first time and not used in similar SRA-approved products.

3.1.R Regional Information

3.1.R.1 Production Documentation

3.1.R.1.1 Executed production documents

A minimum of three batches of commercial scale, should have been manufactured for each strength at the time of submission.

This condition could be exempted by the NMRA if the medicine is a medicine for orphan diseases, a drug considered as “orphan” to Sri Lanka by the NMRA and a drug for emergency situations. The executed production documents of two pilot scale batches should be submitted in this situation and these batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

English translations of executed records should be provided, where relevant

MODULE 4:

NON-CLINICAL STUDY REPORTS

This section of the Guideline is not required for generic products in which a molecule (s) of FPP is registered in NMRA of . In such cases, reference to the list suffices.

4.1 Table of Contents of Module 4

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 PD.

4.2 Study Reports

The study reports should be presented in the following order:

4.2.1 Pharmacology

- 4.2.1.1 Primary Pharmacodynamics
- 4.2.1.2 Secondary Pharmacodynamics
- 4.2.1.3 Safety Pharmacology
- 4.2.1.4 Pharmacodynamic Drug Interactions

4.2.2 Pharmacokinetics

- 4.2.2.1 Analytical Methods and Validation Reports (if separate reports are available)
- 4.2.2.2 Absorption
- 4.2.2.3 Distribution
- 4.2.2.4 Metabolism
- 4.2.2.5 Excretion
- 4.2.2.6 Pharmacokinetic Drug Interactions (nonclinical)
- 4.2.2.7 Other Pharmacokinetic Studies

4.2.3 Toxicology

- 4.2.3.1 Single-Dose Toxicity (in order by species, by route)
- 4.2.3.2 Repeat-Dose Toxicity (in order by species, by route, by duration)
- 4.2.3.3 Genotoxicity
 - 4.2.3.3.1 In vitro
 - 4.2.3.3.2 In vivo (including supportive toxicokinetics evaluations)
- 4.2.3.4 Carcinogenicity (including supportive toxicokinetics evaluations)
 - 4.2.3.4.1 Long-term studies (in order by species, including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
 - 4.2.3.4.2 Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
 - 4.2.3.4.3 Other studies
- 4.2.3.5 Reproductive and Developmental Toxicity (including range-finding studies and supportive toxicokinetics evaluations) [If modified study designs are used, the following sub-headings should be modified accordingly.]
 - 4.2.3.5.1 Fertility and early embryonic development
 - 4.2.3.5.2 Embryo-fetal development

- 4.2.3.5.3 Prenatal and postnatal development, including maternal function
- 4.2.3.5.4 Studies in which the offspring (juvenile animals) are dosed and/or further evaluated
- 4.2.3.6 Local Tolerance
- 4.2.3.7 Other Toxicity Studies (if available)
 - 4.2.3.7.1 Antigenicity
 - 4.2.3.7.2 Immunotoxicity
 - 4.2.3.7.3 Mechanistic studies (if not included elsewhere)
 - 4.2.3.7.4 Dependence
 - 4.2.3.7.5 Metabolites
 - 4.2.3.7.6 Impurities
 - 4.2.3.7.7 Other

4.3 Literature References

MODULE 5:

CLINICAL STUDY REPORTS

This section of the Guideline is applicable only for medicines where a BE study is a requirement and where the medicine is not yet registered in . For FPPs in which the molecule(s) is new to the n market, the applicant should submit full safety and efficacy data as outline in this Guideline.

For multisource generic products having a molecule(s) already registered in and requiring BE study, only section 5.3.3 of Module 5 needs to be supported with actual experimental evidence and where applicable reference to literature can be considered for other section.

For generic products requiring clinical equivalence study, in cases where comparative clinical evidence of a pharmacokinetics (PK) BE study cannot be conducted, section 5.3.4 of Module 5 may be required, to be determined on a case-by-case basis.

The information provided below is not intended to indicate what studies are required for successful registration. It indicates an appropriate organization for the clinical study reports that need to be submitted with the application.

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.

5.1 Table of Contents of Module 5

5.2 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 5.1 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 5.3 below. Use of a different sequence should be noted and explained in an introduction to the tabular listing.

5.3 Clinical Study Reports

5.3.1 Reports of Biopharmaceutical 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 Section 5.3.1, and referenced in Sections 5.3.1.1 and/or 5.3.1.2.

5.3.1.1 Bioavailability (BA) study reports

BA studies in this section should include:

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;

- dosage form proportionality studies; and,
- food-effect studies.

reference to literature suffices for generic products.

5.3.1.2 Comparative BA and 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

- the drug product used in clinical studies supporting effectiveness and the to-be-marketed drug product, the drug product used in clinical studies supporting effectiveness, and the drug product used in stability batches; and,
- similar drug products from different manufacturers.

For in vivo bioequivalence studies and waiver of bioequivalence requirements, WHO guidelines on registration requirements to establish interchangeability at multisource (generic) pharmaceutical products and other relevant WHO guidelines applies.

5.3.1.3 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 section 5.3.1.3. reports of in vitro dissolution tests used for batch quality control and/or batch release should be placed in the Quality section (module 3) of the pd.

5.3.1.4 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 section 5.3.1.4 and referenced in the appropriate individual study reports.

5.3.2 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 (Module 4).

5.3.2.1 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 section 5.3.3.

5.3.2.2 Reports of hepatic metabolism and drug interaction studies

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

5.3.2.3 Reports of studies using other human biomaterials

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

5.3.3 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 sections 5.3.3.1 and 5.3.3.2 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 section 5.3.3.1 to 5.3.3.2, as appropriate.

These studies should characterize 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 sections 5.3.3.1 and/or 5.3.3.2.

Apart from describing mean PK in normal and patient volunteers, PK studies should also describe the range of individual variability. The study of human PK study reports should fulfill the requirements for bioequivalence as described in Annex IV of this Guideline.

5.3.3.1 Healthy subject PK and initial tolerability study reports

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

5.3.3.2 Patient PK and initial tolerability study reports

Reports of PK and initial tolerability studies in patients should be placed in this section. Most of the time for generic products, cross-reference to literature suffices. However, when PK studies are not possible on healthy subjects because of toxicity and other issues, this section should be completed where applicable.

5.3.3.3 Intrinsic factor PK study reports

Reports of PK studies to assess effects of intrinsic factors, should be placed in this section. Reports of PK studies to assess differences in systemic exposure as a result of changes in PK due to intrinsic (e.g., age, gender, racial, weight, height, disease, genetic polymorphism, and organ dysfunction) factors should be placed in this section.

5.3.3.4 Extrinsic factor PK study reports

Reports of PK studies to assess effects of extrinsic factors (e.g., drug-drug interactions, diet, smoking, and alcohol use) factors should be organized in this section.

5.3.3.5 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.

5.3.4 Reports of Human Pharmacodynamic (PhD) Studies

This section of the Guideline does not require experimental evidence for generic products and medicines already registered in Sri Lanka. Exceptions are when meaningful PK studies cannot be conducted as a result of difficulties, such as inadequate measurement of the active pharmaceutical substance in biological fluids. See Annex IV for further clarification.

Reports of studies with a primary objective of determining the PhD 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 section 5.3.5.

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 section 5.3.4.1, and the reports for those studies conducted in patients should be placed in section 5.3.4.2.

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 section 5.3.5, not in section 5.3.4.

5.3.4.1 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.

5.3.4.2 Patient PD and PK/PD study reports

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

5.3.5 Reports of Efficacy and Safety Studies

For generic medicines in which the molecule(s) of FPP are registered in Sri Lanka cross reference to literature will suffice. 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.

In cases where the application includes multiple therapeutic indications, the reports should be organized in a separate section 5.3.5 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 section 5.3.5; if a clinical efficacy study is relevant to multiple indications, the study report should be included in the most appropriate section 5.3.5 and referenced as necessary in other sections 5.3.5, for example, section 5.3.5A, section 5.3.5B.

5.3.5.1 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); or,
- External (historical) control, regardless of the control treatment.

Within each control type, where relevant to the 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 section 5.3.5.1.

Where a pharmacodynamic study contributes to evidence of efficacy, it should be included in section 5.3.5.1. 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 section 5.3.5.1. Controlled safety studies, including studies in conditions that are not the subject of the application, should also be reported in section 5.3.5.1.

5.3.5.2 Study reports of uncontrolled clinical studies

Study reports of uncontrolled clinical studies (e.g., reports of open label safety studies) should be included in section 5.3.5.2. This includes studies in conditions that are not the subject of the marketing application.

5.3.5.3 Reports of analyses of data from more than one study

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.

A report of a detailed analysis of bridging, considering formal bridging studies, other relevant clinical studies, and other appropriate information (e.g., PK and PD information), should be placed in this section if the analysis is too lengthy for inclusion in the Clinical Summary.

5.3.5.4 Other 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; and,
- Reports of controlled or uncontrolled studies not related to the claimed indication.

5.3.6 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 this section.

5.3.7 Case Report Forms and Individual Patient Listings

Case report forms and individual patient data listings are subject to good clinical practice inspection where applicable.

5.4 Literature References

Copies of referenced documents, including important published articles, official meeting minutes, or other regulatory guidance or advice should be provided here. This includes copies of all references cited in the Clinical Overview, and copies of important references cited in the Clinical Summary or in the individual technical reports that were provided in Module 5.

Only one copy of each reference should be provided. Copies of references that are not included here should be immediately available upon request.

APPENDIX 1:**APPLICATION FORM FOR REGISTRATION**

National Medicine Regulatory Authority, 120, Norris Canal Road, Sri Lanka

A. Type of application (check the box applicable)

New Application	
Periodic Re-registration	
Variation to existing marketing authorization (If selected, complete the information below.)	
▪ Previous registration number	
▪ Previous registration condition	
▪ Brief description of change intended	
▪ Reasons for variations	

B. Details on the product

1. Proprietary name (trade name)				
2. Approved generic name (s) (use INN if any)				
3. Standard claimed (BP, Ph.In, Ph. Eur., USP, IH, etc)				
4. Strength(s) per dosage unit				
5. Dosage form				
6. Route of administration				
7. Shelf life (months)				
8. Storage condition				
9. Visual description				
10. Description of container closure				
11. Packaging and pack size				
12. Therapeutic category				
13. Expected schedule of the medicine (Please refer relevant section of the NMRA regulations)	Schedule 1			
	Schedule 2 A			
	Schedule 2 B			
	Schedule 2 C			
	Schedule 3			
14. Complete qualitative and quantitative composition (indicate per unit dosage form, e.g., per tablet, per 5ml, etc.)	Composition	Quantity	Function	Claimed standard
▪ Add/delete as many rows and columns as needed.				

15. Complete qualitative and quantitative composition (indicate per batch in Kg, L, etc.) ▪ Add/delete as many rows and columns as needed.	Composition	Quantity	Function	Claimed standard
16. Statement of similarity and difference of clinical, bio-batch, stability, validation, and commercial batch sizes				
17. Regulatory situation in other country (Provide a list of countries in which this product has been granted a marketing authorization and the restrictions on sale or distribution, e.g., withdrawn from the market, etc.)				

C. Details on the applicant

1. Name	
2. Business address	
3. postal address	
4. Telephone number /Fax number	
5. E mail	
6. Web site	
7. Details	

F. Details on dossiers submitted with the application Section of dossier

	Module	Annex, page number, etc.
1	Module 1	
2	Module 2	
3	Module 3	
4	Module 4	
5	Module 5	

CERTIFICATION BY A RESPONSIBLE PERSON IN THE APPLICANT COMPANY

I, the undersigned, certify that all the information in the accompanying documentation concerning an application for a marketing authorization for;

1.	Proprietary name (trade name)	
2.	Approved generic name(s) (INN)	
3.	Strength(s) per dosage unit	
4.	Dosage form	
5.	Applicant	
6.	Manufacturer	

is correct and true, and reflects the total information available.

Signature	
Name	
Position in company	
Date:	

APPENDIX 2 :

REQUIREMENTS FOR RE-REGISTRATION

A product registration certificate is valid for five years. Therefore, an applicant is required to apply for re-registration within six months prior to the due date.

The application for reregistration should include:

1. Information and dossiers indicated in Module 1 of this Guideline.
2. Summary of the Annual Product Report (APR) for batches produced and marketed in Sri Lanka since the grant of marketing authorization. For the purpose of reregistration, the APR should include all batches produced over the prior five years and a product quality review should be submitted with the objective of verifying the consistency of the quality of the FPP and its manufacturing process.

Rejected batches should not be included in the analysis, but must be reported separately together with the reports of failure investigations, as indicated below.

3. Reviews should be conducted with not less than 10 consecutive batches manufactured over the period of the last 12 months or, where 10 batches were not manufactured in the last 12 months, not less than 25 consecutive batches manufactured over the period of the last 36 months, and should include at least:

- 1) Review of starting and primary packaging materials used in the FPP, especially those from new sources;
- 2) Tabulated review and statistical analysis of quality control and in-process control results;
- 3) Review of all batches that failed to meet established specification(s);
- 4) Review of all critical deviations or non-conformances and related investigations;
- 5) Review of all changes carried out to the processes or analytical methods;
- 6) Review of the results of the stability-monitoring program;
- 7) Review of all quality-related returns, complaints and recalls, including export- only medicinal products;
- 8) Review of the adequacy of previous corrective actions;
- 9) List of validated analytical and manufacturing procedures and their re-validation dates;
- 10) Summary of sterilization validation for components and assembly, where applicable;
- 11) Summary of recent media-fill validation exercises;
- 12) Conclusion of the Annual Product Review;

- 13) Commitment letter that prospective validation will be conducted in the future; and, the Protocol.
4. Tabular summary of any variations notified, accepted, and pending with the Authority since the grant of marketing authorization.
5. Copies of the current API and FPP specifications, duly signed and dated, including the test methods. The specifications should indicate the reference number, version number, effective date, and change history, if any.
6. Samples of actual products

APPENDIX 3: SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the finished pharmaceutical product
2. Qualitative and quantitative composition
3. Pharmaceutical form
4. Clinical particulars
 1. Therapeutic indications
 2. Posology and method of administration
 - a. Children and adolescents (4 to 17 years of age)
 - b. General administration recommendations
 - c. Special dosing considerations in adults
 3. Contraindications
 4. Special warnings and special precautions for use
 5. Interaction with other fpps and other forms of interaction
 6. Use in Pregnancy and lactation
 7. Undesirable effects [*See example below.*]
 8. Overdose
5. Pharmacological properties
 - 5.1 Pharmacodynamic properties
 1. Pharmacotherapeutic group: {group}
 2. ATC code:
 3. Mechanism of action
 4. Pharmacodynamic effects
 - Adults
 - Pediatric patients if recommended
 - 5.2. Pharmacokinetic properties
 1. Absorption
 2. Distribution
 3. Biotransformation

4. Elimination
5. Characteristics in patients

5.3. Preclinical safety data

Data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction

5. Pharmaceutical particulars

1. List of excipients
2. Incompatibilities
3. In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. “This medicinal product must not be mixed with other medicinal products “
4. Shelf life
5. Special precautions for storage
6. Special precautions for usage / preparation before use . Ex:

- Products to be reconstituted -

Method of preparation, the diluent to be use and shelf-life after preparation

- Tablets –

Division of the tablet –state whether tablet can be divided or not

- Special equipment for use, administration or implantation

- Special precautions for disposal and other handling

19. REFERENCE LIST

1. WHO Technical Report Series, No. 863
2. WHO Technical Report Series, Nos. 902
3. WHO Technical Report Series, Nos.908
4. WHO Technical Report Series, No. 929
5. WHO Technical Report Series, No. 943
6. WHO Technical Report Series, No. 953
7. ICH Guidelines Q1A, Q1B, Q1C, Q1D, Q1E, Q3A, Q3B, Q3C, Q5C, Q6A, and Q6B
8. ICH Guidelines Q1A, Q1B, Q1D, Q1E, Q2

20. FEEDBACK

22.1 Staff and customers may provide feedback about this document by emailing info@nmra.gov.lk

