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MINISTRY OF HEALTH

PHARMACY AND POISONS BOARD

COMPENDIUM OF GUIDELINES ON

MEDICINES EVALUATION AND REGISTRATION IN KENYA

AUGUST 2022

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The Pharmacy and Poisons Board acknowledge the effort made by EAC secretariat for the support it offered in the development of the Compendium of Medicines Evaluation and Registration for Medicine Regulation Harmonisation in the East African Community, REF NO EAC/TF-MED/MER/FD/COM/N1R1, 2ND Edition, April 2019, which have now been adopted and customised for use in Kenya.

This Compendium has been adopted, with changes to suit the Kenyan context, to provide guidance to applicants and PPB in managing applications for registration of human medicinal products in the Kenya Market.

This **Compendium of Guidelines on Medicines Evaluation and Registration** has been compiled by the staff of the Product Evaluation and Registration of the Pharmacy and Poisons Board

PART I

GUIDELINES ON SUBMISSION OF DOCUMENTATION FOR REGISTRATION OF HUMAN PHARMACEUTICAL PRODUCTS

ABBREVIATIONS AND ACRONYMS

API	Active Pharmaceutical Ingredient
APIMF	Active Pharmaceutical Ingredient Master File
CEP	Certificate of Suitability to the monograph of Ph Eur monograph
CTD	Common Technical Document
EAC	East Africa Community
EAMRH	East Africa Medicines Registration Harmonization
EA-PSNMRA	East Africa Partner State National Medicines Regulatory Authority
EDQM	European Directorate for the Quality of Medicines
EU	European Union
FPP	Finished Pharmaceutical Product
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonization (of Technical Requirements for Registration Pharmaceuticals for Human Use)
PPB	Pharmacy and Poisons Board
PD	Product Dossier
PHIS	Pharmaceutical Health Information System
PI	Product Information
SDRA	Stringent Drug Regulatory Authority
SmPC	Summary of Product Characteristic

GLOSSARY OF TERMS

Active pharmaceutical ingredient (API)	An active ingredient is any component that provides pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or animals. *(USFDA Glossary of terms, it can be found online at Drugs@FDA Glossary of Terms).*
Active Pharmaceutical 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. (*WHO Glossary of Terms*).
Commitment batches	Production batches of an API or FPP for which the stability studies are initiated or completed post-approval through a commitment made in a regulatory 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.
Existing API	An API that is not considered a new active substance, which has been previously approved through a finished product by a stringent regulatory authority. (*WHO Glossary of Terms*).
Finished pharmaceutical product (FPP)	A finished dosage form of a pharmaceutical product which has undergone all stages of manufacture, including packaging in its final container and labelling. (*WHO Glossary of Terms*).
Generic product	Is a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the

	reference medicinal product has been demonstrated by appropriate bioavailability studies. *(PHIS Glossary 2009, can be found online at:http://phis.goeg.at/index.aspx?alias=phisglossary)*
Innovator medicinal product	Generally, the medicinal product that was first authorised for marketing (normally as a patented product) on the basis of documentation of efficacy, safety and quality. (*WHO Glossary of Terms*).
Manufacturer	A manufacturer is a natural or legal person with responsibility for manufacturing of a medicinal product or active pharmaceutical ingredient. It involves operations such as production, packaging, repackaging, labelling and relabelling of pharmaceuticals. *(PHIS Glossary 2009, can be found on line at: http://phis.goeg.at/index.aspx?alias=phisglossary)*
Market Authorization Holder (MAH)	Marketing Authorization Holder, is an entity or organization responsible for obtaining and holding the marketing authorization for a medicinal product in a specific geographical region, such as a country or a group of countries. The MAH is the party that has the legal and regulatory responsibility for the authorization, distribution, and marketing of the product within the designated region.
Mock-up	A copy of the flat artwork design in full colour, providing a replica of both the outer and immediate packaging, providing a two-dimensional presentation of the packaging/ labelling of the medicine. It is also referred to as a *paper copy* or *computer-generated version*.
Officially recognized	The official recognized pharmacopoeias by PPB are British Pharmacopoeia (BP), European Pharmacopoeia

pharmacopoeia (or compendium)	(Ph Eur.), The International Pharmacopoeia (Ph.Int), Japanese Pharmacopoeia (JP) and United States Pharmacopeia (USP).
On-going 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 retest period (or shelf-life) of the API, or confirm or extend the shelf-life of the FPP. (*WHO Glossary of Terms*).
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. (*WHO Glossary of Terms*).
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 retest period or shelf-life. (*WHO Glossary of Terms*).
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 application.
Specimen	A sample of the actual printed outer and inner packaging materials and package leaflet.

INTRODUCTION

Background

This guideline provides guidance for applicants preparing a Common Technical Document for the Registration of Medicines for Human Use (CTD) for submission to the Pharmacy and Poisons Board (PPB). The document describes how to organise applications based on the Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines on the CTD. According to the CTD format, each application is a collection of documents, grouped into 5 modules. Module 1 prescribes Administrative Information and Prescribing Information requirements which is region specific. The Summaries, Quality, Non-clinical, and Clinical modules have been described in Modules 2 to 5, respectively. Applicants should not modify the overall organisation of the CTD.

If not contained in the bulk of the documentation, any additional data should be included as addenda to the relevant part, together with additional expert comment that may be provided as a supplement to, or incorporated into, the relevant summary, overall summary or overview. Information in these Modules should be present in relevant sections.

For application procedures refer to the Guideline on Procedural Aspects for Application for Market Authorization for Human Medicinal Products.

Scope

These guidelines will assist applicants to prepare applications to register medicinal products for human use. The format for applications is the Common Technical Document (CTD).

These guidelines apply to MA applications for medicinal products containing APIs of synthetic or semi-synthetic origin. Biological, biotechnological and herbal products are not covered by these guidelines.

General Information

The registration of medicine in Kenya is governed by the provisions and requirements of the CAP 244 (hereafter 'the Act') and the regulations and guidelines published in terms thereof.

These guidelines describe the information required for the registration of “medicines” and for an application to amend a registered medicine. The information submitted will be evaluated in terms of the provisions of the Act.

The aim of this guideline is to assist applicants in the preparation of documentation for the registration of medicines for human use. The types of medicine include a new medicine for a new chemical entity (NCE), a multisource (generic) product, a product line extension, a biological medicine, and a complementary medicine.

Medical devices including in vitro diagnostics are addressed in separate guidelines.

It is a legal requirement that data submitted for evaluation should substantiate all claims and should meet technical requirements of quality, safety and efficacy of the product for the purposes for which it is intended. The guidelines are meant to guide the applicant in meeting the requirements of the Act. It is acknowledged, however, that in some instances scientific developments may dictate alternative approaches. When a deviation from a guideline is decided on, a detailed motivation giving the reason(s) for the deviation and justification for the alternative approach should be included in a report submitted with the application.

Whenever there is doubt, applicants are advised to consult the Pharmacy and Poisons Board for confirmation and / or clarification before completing and submitting the application form; refer to the website for contact details.

Applicants should always refer to the current version of the relevant guidelines and the addenda thereto before completing the application form.

Guidelines are constantly evolving due to scientific developments and harmonisation of the requirements of regional and international regulatory authorities. Pharmacy and Poisons Board endeavours to regularly update the

guidelines to reflect current thinking and keep its technical requirements and evaluation policies in line with "best international medicines regulatory practice."

Confidentiality / Secrecy

The officers of the Pharmacy and Poisons Board (PPB) are legally obligated to adhere to the provisions outlined in Section 6 of the Access to Information Act. This section establishes limitations on the right to access information in circumstances where disclosure could substantially harm the commercial interests, including intellectual property rights, of either the PPB or third parties from whom information has been obtained. It also applies in cases where disclosure would breach professional confidentiality as recognized by the law or the regulations of a registered professional association.

Furthermore, in accordance with Section 23(3) of the Public Service Code of Conduct and Ethics from 2016, all public officers, including employees of the PPB, are mandated to take reasonable measures to ensure the adequate protection of confidential or classified information and documents entrusted to their care, preventing improper or inadvertent disclosure

Language

All applications and supporting data submitted to the Pharmacy and Poisons Board should be presented in English (UK). Original documents not in English should be accompanied by an English translation.

Evaluation pathways

Medicines applications for new registrations and variations in Kenya will follow one of four evaluation / review pathways:

i. Full review
ii. Abridged review
iii. Verified review

iv. Recognition

Review pathways (ii), (iii) and (iv) represent reliance-based evaluations. The World Health Organisation defines Good Reliance Practice as "the act whereby the regulatory authority in one jurisdiction may take into account and give significant weight to – i.e. totally or partially rely upon – evaluations performed by another regulatory authority or trusted institution in reaching its own decision. The relying authority remains responsible and accountable for decisions taken, even when it relies on the decisions and information of others." Wherever possible, Pharmacy and Poisons Board will leverage these pathways, relying on the evaluation efforts of Recognised Regulatory Authorities (RRAs) in order to reduce evaluation times. Note that pathways (ii), (iii) and (iv) replace the prior Abbreviated Medicines Review Process (AMRP).

General descriptions of the evaluation pathways are provided below:

Full review

A comprehensive / thorough review of all aspects of the dossier, based primarily on the evaluation of data (and summaries thereof) submitted by the applicant. This is the default routine evaluation pathway for new registrations not previously approved by the Pharmacy and Poisons Board, or where reliance documentation provided to PPB is deemed to be insufficient.

Abridged review

A streamlined review based primarily on un-redacted assessment reports from Recognised Regulatory Authority (RRAs), replacing the need to evaluate all of the data (and summaries thereof) submitted in support of an application.

Verified review

A streamlined review based primarily on verifying, instead of evaluating, information submitted in the application against information which has already been approved by Pharmacy and Poisons Board or a Recognised Regulatory Authority. Note that un-redacted reports are required for verified reviews as a fall-back option for evaluators.

Recognition

A streamlined registration / approval process based on directly recognising the outcome of a review from a RRA with which PPB shares a recognition agreement.

Note: Pharmacy and Poisons Board (PPB) is currently in the process of negotiating recognition agreements with RRAs. Once such an agreement is in place, PPB will publish a framework for the practical implementation thereof. The guiding principle is that applications approved by RRAs with which PPB shares a recognition agreement may not need to be evaluated separately by PPB. Please note that this is not to be confused with collaborative / work-sharing procedures, e.g. PPB.

The abridged and verified review processes do NOT involve an abbreviated application – all data and information required for a full review should be submitted, i.e. the full CTD module structure. Evaluators may still need to review data in the dossier as required (even when presented with un-redacted reports).

PPB's Recognised Regulatory Authorities

To qualify for a reliance evaluation pathway, an application must have been approved by one or more of the RRAs with which PPB aligns itself. PPB's current RRAs include:

- European Medicines Agency Centralised Procedure (EMA CP)
- European Medicines Agency Decentralised Procedure (EMA DCP)
- Health Canada
- Medicines and Health Products Regulatory Agency (MHRA), UK
- Ministry of Health, Labour and Welfare (MHLW), Japan
- Swiss Agency for Therapeutic Products (Swissmedic)
- Therapeutic Goods Administration (TGA), Australia

- US Food and Drug Administration (US FDA)
-

Two additional procedures can be used for reliance/ collaborative review, which are not strictly regulatory authorities:

- World Health Organisation Prequalification (WHO PQ)
- East African Community Medicines Regulatory Harmonization (EAC MRH)
- IGAD Joint Assessment procedure

Fees

The fees payable are published in the Government Gazette and are also available on the website.

Methods of payment: Electronic payment / direct transfer. Cheques are no longer accepted as a method of payment.

Proof of electronic payment / direct transfer must be submitted in a separate and attached in the screening portal with a copy of the letter of application of the relevant submission(s).

To ensure evaluation of the relevant submission(s) a copy of proof of payment both invoice and receipts must be attached with the relevant submission documents.

Samples

All applications for registration must include at least three sample(s) of a unit pack. Where samples are not submitted as indicated in section 7.8, the DRO shall request the applicant to submit a letter of exemption to the Board and assessors shall extract the details of manufacturing and expiry dates from the executed Batch Manufacturing Records (BMR) or certificate of analysis.

Responsibilities of Each Unit

In order to facilitate the correct correspondences, examples of the responsibilities of each unit are outlined below:

Product Evaluation and Registration Directorate

The Product Evaluation and Registration Directorate is responsible for the following:

a) Receiving and acknowledging applications for registration of health products such as Medicine and for amendment of registration dossiers;
b) Receiving correspondence dealing with administrative processes, registration and other application forms, and registration policy information documents and guidelines;
c) Applicant transfers and applicant name and address changes;
d) Cancellations of registered medicines and withdrawal of applications for the registration of medicines
e) Co-ordination of reports on the evaluation of medicines

Medicines Evaluation and Registration (ME&R)

The Medicines Evaluation and Registration Unit is responsible for the

a) Evaluation of Quality of the drug substance (API) and drug product (finished pharmaceutical product);
b) Bioequivalence of generic medicines to their innovator counter parts.
c) Evaluation of clinical and pre-clinical data;
d) Biological new registration applications and responses to resolutions, and matters pertaining to biological medicines during review for registration;
e) Evaluation of technical changes to registered biological medicines and "old" biological medicine
f) Evaluation of clinical aspects of the Professional Information and relevant changes to Professional Information for biological medicines;

Inspectorate and law enforcement

The Inspectorate and Law Enforcement Unit is responsible for

a) Inspection and evaluation of sites for the manufacturing, packing, and testing of medicines nationally and internationally, as well as inspection and evaluation of all storage and distribution sites for medicines;

b) Investigation of complaints regarding registered and unregistered medicines;
c) Monitoring compliance to the Act and prosecution in case of non-compliance;
d) Monitoring the importation and exportation of medicines in consultation with customs authorities;
e) Evaluation of products in the market and any changes thereto.

Clinical trials

The Clinical Trials Unit is responsible for the evaluation of

a) Clinical trial applications and clinical trial amendments;

b) Reports of adverse events arising from a clinical trial;

c) applications for named patient use of unregistered medicines;

d) applications for the use of unregistered medicines for clinical trial purposes.

MODULE 1: ADMINISTRATIVE INFORMATION AND PRODUCT INFORMATION

Module 1 should contain all administrative documents (for example, application forms and certifications), labelling, general correspondence and annexes (environmental assessments, antibiotic resistance and overseas evaluation reports), as needed. Documents should be organized in the order listed below. Generally, all of the documents in Module 1, other than the annexes, can be provided in a single volume. The annexes to the module should be submitted in separate volumes. Official language is English as a mandatory language for all medicines.

Products shall be evaluated on a First in First out (FIFO) basis and the timeline for review and approval should be within 12 months.

1.1 Comprehensive table of contents for all modules

Module 1 should include a comprehensive table of contents for the entire application. The comprehensive table of contents should include a complete list of all documents provided in the application by module. In the table of contents, the location of each document should be identified by referring to the volume numbers that contain the relevant documents and any tab identifiers. In general, the name for the tab identifier should be the name of the document.

1.2 Cover letter

Applicants should include a cover letter with all applications. A copy of the letter should be placed at the beginning of Module 1. The cover letter shall be signed by the Market Authorization Holder (Refer Annex I).

1.3 Application form

An application to register a medicinal product for human use must be accompanied by a completed application form (annex II). The application form should be dully filled with relevant information and attachments, dated signed and stamped appropriately.

1.4 Product Information

Provide copies of all package inserts, labels and any information intended for distribution with the product to the patient.

If the Summary Product Characteristics (SmPC), has not been approved from SDRA at the time the application is submitted to PPB, a draft document may be included. The approved SmPC from SDRA should then be submitted to PPB as they become available.

1.4.1 Prescribing information (Summary of Product Characteristics)

All prescription medicines should be accompanied by SmPC.

Refer to the Guideline on Summary of Product Characteristics, Patient Information Leaflet, and Labelling, HPT/PER/GUD/079.

1.4.2 Container labelling

Product should be labeled as prescribed.

Refer to the Guideline on Summary of Product Characteristics, Patient Information Leaflet, and Labelling, (HPT/PER/GUD/079).

1.4.3 Patient information leaflet (PIL)

All medicinal preparations with potential for long term use and self-administered injections and Over the Counter (OTC) must contain a patient information leaflet. Languages used for PIL and labelling should be clearly expressed in English and French.

Refer to the Guideline on Summary of Product Characteristics, Patient Information Leaflet, and Labelling, (HPT/PER/GUD/079).

1.4.4 Mock-ups and specimens

If the product applicant has a specimen or mock-up of the sample(s) presentation of the medicine available at the time of initial application, it should be included in Module1.4.4.

If there are multiple strengths and/or pack sizes, one representative specimen or mock-up for each will be sufficient. If batch number and expiry date are to be printed on the label during packaging, a statement to this effect should accompany the labels. If mock-ups or specimens are not available at the time of initial application, a text version may be submitted, however, mock-ups or specimens must be submitted to PPB, during the evaluation process and prior to finalization of the application.

1.5 Information about the experts

Experts must provide detailed reports of the documents and particulars, which constitute Modules 3, 4 and 5.

The requirement for these signed Expert Reports may be met by providing:

- The Quality Information Summary
- The Quality Overall Summary, Non-clinical Overview / Summary and Clinical Overview / Summary in Module 2,
- A declaration signed by the experts in Module 1.6.

- Brief information on the educational background, training and occupational experience of the experts in Module 1.6.

Experts should indicate in their declarations the extent, if any of their professional or other involvement with the applicant / dossier owner and confirm that the report has been prepared by them or if not, any assistance provided and by whom. Reports should be based on an independent assessment of the dossier and references must be provided for any additional claims not supported by the dossier. A sample expert declaration form is provided as **Annex III**.

Additionally, Quality Information Summary as provided under **Annex IV** should be submitted.

1.6 Certificates of Suitability of monographs of the European pharmacopoeia (CEP) or Letter of Access to EAC-APIMF

If a CEP is available, the finished product applicant should present copy of CEP in module 1.7.

Applicant should provide the Letter of Access to CEP or Letter of Access to EAC-APIMF as appropriate from the API manufacturer. These letters should be included in Module 1.7. (Refer **Annex V and Annex VI**)

1.7 Good Manufacturing Practice (GMP)

For all medicines, irrespective of the country of origin, all key manufacturing and/or processing steps in the production of active pharmaceutical ingredient ingredients and finished pharmaceutical products must be performed in plants that comply with PPB GMP guidelines. Attach a WHO- certificate of GMP. For more information on GMP requirements and application for GMP inspection, refer PPB Guidelines on Good Manufacturing Practice for more guidance.

If available at the time of submission of application, GMP certificates from PPB or evidence of application for GMP inspection should be submitted in Module 1.15.

1.8 Good Clinical Practice (GCP) or Good Laboratory Practice (GLP)

Provide evidence such as accredited certificate for GCP or GLP for the sites participating in the clinical studies.

1.9 Regulatory status

1.9.1 Registration status from countries with Stringent Drug Regulatory Authorities (SDRAs)

Provide registration status of the medicinal product applied for registration in the countries with SDRAs and attach evidence(s) for the same.

1.9.2 Registration status in other regions

Provide registration status/certificate of the medicinal product applied for registration in other regions and attach evidence(s) for the same.

1.9.3 List of countries in which a similar application has been submitted

The applicant should provide, in Module 1.9.1 of the dossier, a list of countries in which a similar application has been submitted, dates of submission (if available) and the status of these applications. This should detail approvals (with indications) and deferrals, withdrawals and rejections with reasons in each case.

1.9.4 Statement on whether an application for the product has been previously rejected, withdrawn or repeatedly deferred by PPB

Applicant must declare whether a marketing application for the medicine has been rejected prior to submission of the application to PPB. If the medicine has been rejected, repeatedly deferred, withdrawn or suspended then reasons must be stated.

1.10 Evidence of API and/or FPP prequalified by WHO

If evidence indicating that the active pharmaceutical ingredient and/or finished pharmaceutical product are prequalified by WHO is available, it should be presented in Module 1.

1.11 Manufacturing and Marketing authorization

Submit a Certificate of Pharmaceutical Product in format recommended by the World Health Organization together with a valid Manufacturing Authorization for pharmaceutical production. If available, evidence for prequalification of medicinal product by WHO should be submitted.

1.12 Product samples

Sufficient number of samples should be submitted together with the application. The quantity of samples should be adequate to carry out full specification analysis plus one repeat.

Batch number, Manufacturing Date and Expiry Date should be dynamically printed on packages for all medicines except in situations where there is space restriction, the details can be on secondary packages with the primary pack having at least the batch number and expiry date. Pre-printing of the batch number, manufacturing date and Expiry Date will not be acceptable.

MODULE 2: OVERVIEW & SUMMARIES

2.1 Table of contents of Module 2

A table of contents for module 2 should be provided.

2.2 CTD Introduction

2.3 Quality Overall Summary (QOS)

The quality overall summary (QOS) is a summary that follows the scope and the outline of the Body of Data in Module 3.

The QOS should not include information, data or justification that was not already included in Module 3 or in other parts of the common technical document (CTD). Complete Annex VII following the guidance below should be submitted.

2.3.S: Active pharmaceutical ingredient (name, manufacturer)

2.3.S.1 General Information (name, manufacturer)

Information from 3.2.S.1 should be included.

2.3.S.2 Manufacture (name, physical address)

Information from 3.2.S.2 should be included.

Information on the manufacturer:

- A brief description of the manufacturing process and the controls
- A flow diagram, as provided in 3.2.S.2.2;
- A description of the Source and Starting Material and raw materials of biological origin used in the manufacture of the API, as described in 3.2.S.2.3;
- Highlight critical process intermediates, as described in 3.2.S.2.4;
- A description of process validation and/or evaluation, as described in 3.2.S.2.5.

2.3.S.3 Characterization

A summary of the interpretation of evidence of structure and isomerism, as described in 3.2.S.3.1.

A tabulated summary of the data provided in 3.2.S.3.2, with graphical representation, where appropriate should be included.

2.3.S.4 Control of Drug Substance

A brief summary of the justification of the specification(s), the analytical procedures, and validation should be included.

Specification from 3.2.S.4.1 should be provided.

A tabulated summary of the batch analyses from 3.2.S.4.4, with graphical representation where appropriate, should be provided.

2.3.S.5 Reference Standards or Materials

Information from 3.2.S.5 (tabulated presentation, where appropriate) should be included.

2.3.S.6 Container Closure System

A brief description and discussion of the information, from 3.2.S.6 should be included.

2.3.S.7 Stability

This section should include a summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions, the proposed storage conditions, retest date or shelf-life, where relevant, as described in 3.2.S.7.1.

The post-approval stability protocol, as described in 3.2.S.7.2, should be included.

A tabulated summary of the stability results from 3.2.S.7.3, with graphical representation where appropriate, should be provided.

2.3.P Finished Pharmaceutical Product (name, dosage form)

2.3.P.1 Description and Composition of the Drug Product (name, dosage form)

Information from 3.3.P.1 should be provided.

Composition from 3.3.P.1 should be provided.

2.3.P.2 Pharmaceutical Development

A discussion of the information and data from 3.3.P.2 should be presented.

A tabulated summary of the composition of the formulations used in clinical trials and a presentation of dissolution profiles should be provided, where relevant.

2.3.P.3 Manufacture (name, physical address)

Information from 3.3.P.3 should include:

Information on the manufacturer

A brief description of the manufacturing process and the controls that are intended to result in the routine and consistent production of product of appropriate quality.

A flow diagram, as provided under 3.3.P.3.3.

A brief description of the process validation and/or evaluation, as described in 3.3.P.3.5.

2.3.P.4 Control of Excipients

A brief summary on the quality of excipients, as described in 3.3.P.4, should be included.

2.3.P.5 Control of Drug Product

A brief summary of the justification of the specification(s), a summary of the analytical procedures and validation, and characterization of impurities should be provided. Specification(s) from 3.3.P.5.1 should be provided.

A tabulated summary of the batch analyses provided under 3.3.P.5.4, with graphical representation where appropriate should be included.

2.3.P.6 Reference Standards or Materials

Information from 3.3.P.6 (tabulated presentation, where appropriate) should be included.

2.3.P.7 Container Closure System

A brief description and discussion of the information in 3.3.P.7 should be included.

2.3.P.8 Stability

A summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions of the stability studies and analysis of data should be included. Conclusions with respect to storage conditions and shelf-life and, if applicable, in-use storage conditions and shelf-life should be given.

Stability studies should be provided for each pack type applied for registration.

A tabulated summary of the stability results from 3.3.P.8.3, with graphical representation where appropriate, should be included.

The post-approval stability protocol, as described in 3.3.P.8.2, should be provided.

2.4 Non-Clinical overview

The non-clinical overview should provide an integrated overall analysis of the information in the Common Technical Document. In general, the Nonclinical Overview should not exceed about 30 pages.

The non-clinical overview should be presented in the following sequence:

- Overview of the nonclinical testing strategy
- Pharmacology
- Pharmacokinetics
- Toxicology
- Integrated overview and conclusions
- List of literatures references

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

The Integrated Overview and Conclusions should clearly define the characteristics of the human pharmaceutical as demonstrated by the

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

Refer ICH Guidance on the Common Technical Document for the registration of pharmaceuticals for human use: Safety for guidance on the format and the content of this part.

Generic products are generally exempted in this module; however, in some cases such as changes in safety impurity profile, the safety assessment studies should be conducted.

2.5 Clinical overview

The Clinical Overview is intended to provide a critical analysis of the clinical data in the Common Technical Document. The Clinical Overview will necessarily refer to application data provided in the comprehensive Clinical Summary, the individual clinical study reports (ICH E3), and other relevant reports; but it should primarily present the conclusions and implications of those data, and should not recapitulate them. Specifically, the Clinical Summary should provide a detailed factual summarization of the clinical information in the CTD, and the Clinical Overview should provide a succinct discussion and interpretation of these findings together with any other relevant information.

The clinical Overview should be presented in the following sequence

- Product Development Rationale
- Overview of Biopharmaceutics
- Overview of Clinical Pharmacology
- Overview of Efficacy
- Overview of Safety
- Benefits and Risks Conclusions
- Literature References

Refer ICH Guidance on the Common Technical Document for the registration of pharmaceuticals for human use: Efficacy (M4E) for guidance on the format and the content of this part.

2.6 Nonclinical Written and Tabulated Summaries

The following order is recommended:

- Introduction
- Written Summary of Pharmacology
- Tabulated Summary of Pharmacology
- Written Summary of Pharmacokinetics
- Tabulated Summary of Pharmacokinetics
- Written Summary of Toxicology
- Tabulated Summary of Toxicology

Refer ICH Guidance on the Common Technical Document for the registration of pharmaceuticals for human use: Safety for guidance on the format and the content of this part

For generic products are generally exempted in this module; however, in some cases such as changes in safety impurity profile, the safety assessment studies should be conducted.

2.7 Clinical Summary

The Clinical Summary is intended to provide a detailed, factual summarization of all of the clinical information in the Common Technical Document. This includes information provided in ICH E3 clinical study reports; information obtained from any meta-analyses or other cross-study analyses for which full reports have been included in Module 5; and post-marketing data for products that have been marketed in other regions.

Refer ICH Guidance on the Common Technical Document for the registration of pharmaceuticals for human use: refer to Efficacy for guidance on the content of this section.

MODULE 3: QUALITY

3.1 Table of contents of Module 3

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

3.2 Body of data

3.2.S Active pharmaceutical ingredient (API))

The API information can be submitted to PPB in the order of preference in one of the following four options:

a) Option1: Certificate of suitability of European Pharmacopeia (CEP);
b) Option 2: Active pharmaceutical ingredient pre-qualified by WHO;
c) Option 3: PPB Active Pharmaceutical Ingredient Master File (PPB-APIMF);
d) Option 4: Full details in the Product Dossier (PD);

The applicant should clearly indicate at the beginning of the API section in the Marketing Authorization (MA) application and in the QOS how the information on the API for each API manufacturer is being submitted.

Where reference is made to CEP, the finished product applicant must have written permission to access the CEP from the CEP holder. Applicant should provide the *Letter of Access to CEP,* as appropriate from API manufacturer **(**Refer **Annex V).** Letter of access should be included in Module 1.7.

Where reference is made to PPB-APIMF, the finished product applicant must have written permission to access the APIMF from the company that supplied the APIMF and must provide the APIMF file number to the PPB-PPB. Applicant should provide the *Letter of Access to EAC-APIMF,* as appropriate from API manufacturer **(**Refer **Annex VI).** Letter of access should be included in Module 1.7.

The applicant's open part of the APIMF should be included in Module 3.2.S of the Quality documentation presented in the CTD format. The API manufacturer's restricted (closed) part is supplied to PPB-PPB directly by the API manufacturer when required.

The API information submitted by the applicant/FPP manufacturer should include the following for each of the options used.

Option 1: Certificate of suitability of European Pharmacopeia (CEP)

A complete copy of the CEP (including any annexes) should be provided in Module 1. The declaration of access for the CEP should be dully filled out by the CEP holder on behalf of the FPP manufacturer or applicant to the PPB who refers to the CEP.

In addition, a written commitment should be included that the applicant will inform PPB 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 QOS-PD:

a) 3.2.S.1.3 General properties – discussions on any additional applicable physicochemical and other relevant API properties that are not controlled by the CEP and Ph.Eur monograph, e.g. solubilities and polymorphs as per guidance in this section.
b) 3.2.S.3.1 Elucidation of structure and other characteristics – studies to identify polymorphs (exception: where the CEP specifies a polymorphic form) and particle size distribution, where applicable, as per guidance in this section
c) 3.2.S.4.1 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.
d) 3.2.S.4.2/3.2.S.4.3 Analytical procedures and validation – for any tests in addition to those in the CEP and Ph.Eur monograph.
e) 3.2.S.4.4 Batch analysis – results from two batches of at least pilot scale, demonstrating compliance with the FPP manufacturer's API specifications.
f) 3.2.S.5 Reference standards or materials – information on the FPP manufacturer's reference standards.

g) 3.2.S.6 Container-closure system – specifications including descriptions and identification of primary packaging components.
h) 3.2.S.7 Stability – exception: where the CEP specifies a re-test period that is the same as or of longer duration than the re-test period proposed by the applicant.
i) In the case of sterile APIs, data on the sterilization process of the API, including validation data, should be included in the PD.

Option 2: Active pharmaceutical ingredient pre-qualified by WHO

A complete copy of the Confirmation of API prequalification document should be provided in Module 1, together with the duly filled out authorization box in the name of the FPP manufacturer or applicant.

The applicant should supply the following information in the dossier, with data summarized in the QOS-PD: -

a) 3.2.S.1.3 General properties – discussions on any additional applicable physicochemical and other relevant API properties that are not controlled by the API manufacturer's specifications, e.g., solubilities and polymorphs according to the guidance in this section
b) 3.2.S.2 – if the sterility of the FPP is based upon the sterile manufacture of the API then data on the sterilization process together with full validation data should be provided.
c) 3.2.S.3.1 Elucidation of structure and other characteristics – studies to identify polymorphs and particle size distribution, where applicable, according to the guidance in this section.
d) 3.2.S.4.1 Specification – the specifications of the FPP manufacturer including all tests and limits of the API manufacturer's specifications and any additional tests and acceptance criteria that are not controlled by the API manufacturer's specifications such as polymorphs and/or particle size distribution.
e) 3.2.S.4.2/3.2.S.4.3 Analytical procedures and validation – any methods used by the FPP manufacturer in addition to those in the API manufacturer's specifications.

f) 3.2.S.4.4 Batch analysis – results from two batches of at least pilot scale, demonstrating compliance with the FPP manufacturer's API specifications.
g) 3.2.S.5 Reference standards or materials – information on the FPP manufacturer's reference standards.
h) 3.2.S.7 Stability – data to support the retest period if either the proposed retest period is longer or the proposed storage conditions are at a higher temperature or humidity to that of the prequalified API.

Option 3: PPB Active Pharmaceutical Ingredient Master File (PPB-APIMF)

Option 3 (a): A copy of confirmation of registration of the API by PPB PPBs provided in Module 1, together with the duly filled out authorization box in the name of the FPP manufacturer or applicant.

The applicant should supply the following information in the dossier, with data summarized in the QOS-PD: -

a) 3.2.S.1.3 General properties – discussions on any additional applicable physicochemical and other relevant API properties that are not controlled by the API manufacturer's specifications, e.g. solubilities and polymorphs according to the guidance in this section.
b) 3.2.S.2 – if the sterility of the FPP is based upon the sterile manufacture of the API then data on the sterilization process together with full validation data should be provided.
c) 3.2.S.3.1 Elucidation of structure and other characteristics – studies to identify polymorphs and particle size distribution, where applicable, according to the guidance in this section.
d) 3.2.S.4.1 Specification – the specifications of the FPP manufacturer including all tests and limits of the API manufacturer's specifications and any additional tests and acceptance criteria that are not controlled by the API manufacturer's specifications such as polymorphs and/or particle size distribution.
e) 3.2.S.4.2/3.2.S.4.3 Analytical procedures and validation – any methods used by the FPP manufacturer in addition to those in the API manufacturer's specifications.

f) 3.2.S.4.4 Batch analysis – results from two batches of at least pilot scale, demonstrating compliance with the FPP manufacturer's API specifications.
g) 3.2.S.5 Reference standards or materials – information on the FPP manufacturer's reference standards.
h) 3.2.S.7 Stability – data to support the retest period if either the proposed retest period is longer or the proposed storage conditions are at a higher temperature or humidity to that of the API approved by the PPBs.

Option 3 (b): Full details on the API information submitted by the API manufacturer, provided that the APIMF contains all information listed under Module 3.

It is the responsibility of the applicant to ensure that the API manufacturer's APIMF restricted part is supplied to PPB directly by the API manufacturer when required. A copy of the letter of access should be provided in the product dossier in Module 1.

APIMF holders can use the guidance provided for the option "Full details in the" for preparation of the relevant sections of the Open and Restricted parts of their APIMFs.

Option 4: Full details by completing Section 3.2.S.1 - 3.2.S.7 of these guidelines

Information on the 3.2.S Active pharmaceutical ingredient sections, including full details of chemistry, manufacturing process, quality controls during manufacturing and process validation for the API, should be submitted in the FPP dossier as outlined in the subsequent sections of this guideline.

3.2.S.1 General information

3.2.S.1.1 Nomenclature

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

- International Non-proprietary Name (INN); (Recommended)
- Compendial name, if relevant;
- Chemical name(s);

- Company or laboratory code;
- Other non-proprietary name(s) (e.g., national name, United States Adopted Name (USAN), British Approved Name (BAN)); and Chemical Abstracts Service (CAS) registry number.

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

3.2.S.1.2 Structure

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

This information should be consistent with that provided in section 3.2.S.1.1. For APIs existing as salts, the molecular mass of the free base or acid should also be provided.

3.2.S.1.3 General properties

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

This information can be used in developing the specifications, in formulating FPPs and in the testing for release and stability purposes.

The physical and chemical properties of the API should be discussed including the physical description, solubilities 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. (see table in the QOS). This list is not intended to be exhaustive, but provides an indication as to the type of information that could be included.

Some of the more relevant properties to be considered for APIs are discussed below in greater detail.

Physical description

The description should include appearance, colour and physical state. Solid forms should be identified as being crystalline or amorphous (see 3.2.S.3.1 for further information on API solid forms).

Solubilities/quantitative aqueous pH solubility profile

The following should be provided for all options for the submission of API data:

The solubilities in a number of common solvents should be provided (e.g. water, alcohols, dichloromethane, acetone).

The solubilities over the physiological pH range (pH 1.2 to 6.8) in several buffered media should be provided in mg/ml. If this information is not readily available (e.g. literature references), it should be generated in-house.

For solid oral dosage forms, the dose/solubility volume should be provided as determined by:

$$\text{Dose/solubility volume} = \frac{\text{largest dosage strength (mg)}}{\text{the minimum concentration of the drug (mg/ml)*}}$$

Corresponding to the lowest solubility determined over the physiological pH range (pH 1.2 to 6.8) and temperature (37 ± 0.5 °C).

As per the Biopharmaceutics Classification System (BCS), highly soluble (or highly water- soluble) APIs are those with a dose/solubility volume of less than or equal to 250 ml.

For example, compound A has as its lowest solubility at 37 ± 0.5 °C, 1.0 mg/ml at pH 6.8 and is available in 100 mg, 200 mg and 400 mg strengths. This API would not be considered a BCS highly soluble API as its dose/solubility volume is greater than 250 ml (400 mg/1.0 mg/ml=400 ml).

Polymorphism

a) The polymorphic form(s) present in the proposed API should be listed in section 3.2.S.1.3;
b) The description of manufacturing process and process controls (3.2.S.2.2) should indicate which polymorphic form is manufactured,

where relevant; the literature references or studies performed to identify the potential polymorphic forms of the API, including the study results, should be provided in section 3.2.S.3.1; and if a polymorphic form is to be defined or limited (e.g. for APIs that are not *BCS highly soluble* and/or where polymorphism has been identified as an issue), details should be included in 3.2.S.4.1 through 3.2.S.4.5.

Additional information is included in the referenced sections of this guideline.

Particle size distribution

Studies performed to identify the particle size distribution of the API should be provided in section 3.2.S.3.1 (refer to this section of this guideline for additional information).

Information from literature

Supportive data and results from specific studies or published literature can be included within or attached to this section.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s) (name, physical address)

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, labelling, testing and storage of the API should be listed. If certain companies are responsible only for specific steps (e.g. milling of the API) it should be clearly indicated.

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 product dossier Module 1.

3.2.S.2.2 Description of manufacturing process and process controls

The description of the API manufacturing process represents the applicant's commitment for the manufacture of the API. Information should be provided to adequately describe the manufacturing process and process controls. For example, 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.

A sequential procedural narrative of the manufacturing process should be submitted. The narrative should include, for example, quantities of raw materials, solvents, catalysts and reagents reflecting the representative batch scale for commercial manufacture, identification of critical steps, process controls, equipment and operating conditions (e.g. temperature, pressure, pH, time).

Alternate processes should be explained and described with the same level of detail as the primary process. Reprocessing steps should be identified and justified. Any data to support this justification should be either referenced or filed in 3.2.S.2.5.

The following requirements apply to the second option for submission of API information, where full details are provided in the dossier.

The API starting material should be fully characterized with respect to identity and purity. The starting material for synthesis defines the starting point in the manufacturing process for an API to be described in an application. The applicant should propose and justify which substances should be considered as starting materials for synthesis. See section 3.2.S.2.3 for further guidance.

The recovery of materials, if any, should be described in detail with the step in which they are introduced into the process. Recovery operations should be adequately controlled such that impurity levels do not increase over time. For recovery of solvents, any processing to improve the quality of the recovered solvent should be described. Regarding recycling of filtrates (mother liquors) to obtain second crops, information should be available on maximum holding

times of mother liquors and maximum number of times the material can be recycled. Data on impurity levels should be provided to justify recycling of filtrates.

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.

All solvents used in the manufacture (including purification and/or crystallization step(s)) should be clearly identified. Solvents used in the final steps should be of high purity. Use of recovered solvents in the final steps of purification and/or crystallization is not recommended.

Where particle size is considered a critical attribute (see 3.2.S.3.1 for details), the particle size reduction method(s) (milling, micronization) should be described.

Justification should be provided for alternate manufacturing processes. Alternate processes should be explained with the same level of detail as the primary process. It should be demonstrated that batches obtained by the alternate processes have the same impurity profile as the principal process. If the obtained impurity profile is different, it should be demonstrated to be acceptable according to the requirements described under S.3.2.

3.2.S.2.3 Control of materials

Materials used in the manufacture of the API (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 meet standards appropriate for their intended use should be provided.

In general, the starting material for synthesis described in the marketing authorization dossier should:

- Be a synthetic precursor of one or more synthesis steps prior to the final API intermediate. Acids, bases, salts, esters and similar

derivatives of the API, as well as the racemate of a single enantiomer API, are not considered final intermediates;

- Be a well characterized, isolated and purified substance with its structure fully elucidated including its stereochemistry (when applicable);
- Have well-defined specifications that include among others one or more specific identity tests and tests and limits for assay and specified, unspecified and total impurities; and
- Be incorporated as a significant structural fragment into the structure of the API.

Copies of the specifications for the materials used in the synthesis, extraction, isolation and purification steps should be provided in the PD, including starting materials, reagents, solvents, catalysts and recovered materials. Confirmation should be provided that the specifications apply to materials used at each manufacturing site. A certificate of analysis of the starting material for synthesis should be provided. A summary of the information on starting materials should be provided in the QOS-PD.

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.

3.2.S.2.4 Controls of critical steps and intermediates

Critical steps: Tests and acceptance criteria (with justification including experimental data) performed at critical steps identified in 3.2.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.

The critical steps should be identified. These can be among others: steps where significant impurities are removed or introduced, steps introducing an

essential molecular structural element such as a chiral centre or resulting in a major chemical transformation, steps having an impact on solid-state properties and homogeneity of the API that may be relevant for use in solid dosage forms.

Specifications for isolated intermediates should be provided and should include tests and acceptance criteria for identity, purity and assay, where applicable.

3.2.S.2.5 Process validation and/or evaluation

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

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. Alternate processes should be justified and described.

3.2.S.3 Characterization

3.2.S.3.1 Elucidation of structure and other characteristics

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.

<u>Elucidation of structure</u>

The MA application 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 QOS should include a list of the studies performed and a conclusion from the studies (e.g. if 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 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) run concomitantly with a pharmacopeial reference standard.

Isomerism/Stereochemistry

Where the potential for stereoisomerism exists, a discussion should be included of the possible isomers that can result from the manufacturing process and the steps where chirality was introduced. The identity of the isomeric composition of the API to that of the API in the comparator product should be established. Information on the physical and chemical properties of the isomeric mixture or single enantiomer should be provided, as appropriate. The API specification should include a test to ensure isomeric identity and purity.

The potential for inter-conversion of the isomers in the isomeric mixture, or racemization of the single enantiomer should be discussed.

When a single enantiomer of the API is claimed for non-pharmacopeial APIs, unequivocal proof of absolute configuration of asymmetric centres should be provided such as determined by X-ray of a single crystal.

If, based on the structure of the API, there is not a potential for stereoisomerism, it is sufficient to include a statement to this effect.

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 non-

stoichiometric 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 processability, 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.

Applicants and API manufacturers are expected to have adequate knowledge about the polymorphism of the APIs used and/or produced. Information on polymorphism can come from the scientific literature, patents, compendia or other references to determine if polymorphism is a concern, e.g. for APIs that are not BCS highly soluble. In the absence of published data for APIs that are not BSC highly soluble, polymorphic screening will be necessary to determine if the API can exist in more than one crystalline form. Polymorphic screening is generally accomplished via crystallization studies using different solvents and conditions.

There are a number of methods that can be used to characterize the polymorphic forms of an API. Demonstration of a non-equivalent structure by single crystal X-ray diffraction is currently regarded as the definitive evidence of polymorphism. X-Ray diffraction can also be used to provide unequivocal proof of polymorphism. Other methods, including microscopy, thermal analysis (e.g. DSC, thermal gravimetric analysis and hot-stage microscopy) and spectroscopy (e.g. IR, Raman, solid-state nuclear magnetic resonance (ssNMR) is helpful to further characterize polymorphic forms. Where polymorphism is a concern, the applicants/ manufacturers of APIs should demonstrate that a suitable method, capable of distinguishing different polymorphs, is available to them.

Polymorphism can also include solvation or hydration products (also known as pseudopolymorphs). If the API is used in a solvated form, the following information should be provided:

a) Specifications for the solvent-free API in 3.2.S.2.4, if that compound is a synthetic precursor;
b) Specifications for the solvated API including appropriate limits on the weight ratio API to solvent (with data to support the proposed limits);
c) A description of the method used to prepare the solvate in 3.2.S.2.2.

Particle size distribution

For APIs whose particle size distribution will have influence on FPP processability, stability, content uniformity, dissolution and bioavailability, specifications should include controls on the particle size distribution.

3.2.S.3.2 Impurities

Information on impurities should be provided.

Details on the principles for the control of impurities (e.g. reporting, identification and qualification) are outlined in the ICH Q3A and Q3C impurity guidelines. 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.

Refer: ICH Q3A: Impurities in New Drug Substances and ICH Q3C Impurities: Guideline for Residual Solvents

3.2.S.4 Control of the API

3.2.S.4.1 Specification

The specification for the API 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 marketing authorization dossier, 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 QOS template under the headings tests, acceptance criteria and analytical procedures (including types, sources and versions for the methods).

a) The standard declared by the applicant could be an officially recognized compendial standard (BP, JP, Ph.Eur, Ph.Int. and USP) or a house (manufacturer's) standard.
b) The specification reference number and version (e.g. revision number and/or date) should be provided for version control purposes.
c) 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 (BP, JP, Ph.Eur, Ph.Int, USP, 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.

3.2.S.4.2 Analytical procedures

The analytical procedures used for testing the API 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 compendial analytical procedures.

3.2.S.4.3 Validation of analytical procedures

Analytical validation information, including experimental data for the analytical procedures used for testing the API, should be provided.

Copies of the validation reports for the 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.

Tables should be used to summarize the validation information of the analytical procedures of the FPP manufacturer for determination of residual solvents, assay and purity of the API, in section 2.3.S.4.3 of the QOS. The validation data for other methods used to generate assay and purity data in the PD can be summarized in 2.3.S.4.4 (c) or 2.3.S.7.3 (b) of the QOS.

The compendial 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 that were not considered during the development of the monograph. Therefore, the monograph and compendial method should be demonstrated suitable to control the impurity profile of the API from the intended source(s).

In general, verification is not necessary for compendial API assay methods. However, the specificity of a specific compendial assay method should be demonstrated if there are any potential impurities that are not specified in the compendial monograph. If an officially recognized compendial 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 compendial standard is claimed and an in-house method is used in lieu of the compendial method (e.g. for assay or for specified impurities), the equivalency of the in-house and compendial 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.

Refer to ICHQ2: Validation of Analytical Procedures: Text and Methodology for more guidance

3.2.S.4.4 Batch analyses

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.

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. This data is used to evaluate consistency in API quality. The FPP manufacturer's test results should be summarized in the QOS.

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).

3.2.S.4.5 Justification of specification

Justification for the API 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 compendial standard(s), etc. If the officially recognized compendial 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.

Refer ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, for more guidance

3.2.S.5 Reference standards or materials

Information on the reference standards or reference materials used for testing of the API should be provided. 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 suitable primary reference standard should be obtained from an officially recognized pharmacopeial source (BP, JP, Ph.Eur, Ph.Int, USP) where one exists and the lot number should be provided. Primary reference standards from officially recognized pharmacopeial sources do not need further structural elucidation.

Otherwise, a primary standard may be a batch of the API that has been fully characterized (e.g. by IR, UV, NMR, MS analyses). Further purification techniques may be needed to render the material acceptable for use as a chemical reference standard. The purity requirements for a chemical reference substance depend upon its intended use. A chemical reference substance proposed for an identification test does not require meticulous purification, since the presence of a small percentage of impurities in the substance often has no noticeable effect on the test. On the other hand, chemical reference substances that are to be used in assays should possess a high degree of purity (such as 99.5% on the dried or water-/solvent-free basis). Absolute content of the primary reference standard must be declared and should follow the scheme:

100% minus organic impurities (quantitated by an assay procedure, e.g. HPLC, DSC, etc.) minus inorganic impurities minus volatile impurities by loss on drying (or water content minus residual solvents).

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. A secondary reference standard is often characterized and evaluated for its intended purpose with additional procedures other than those used in routine testing (e.g. if additional solvents are used during the additional purification process that are not used for routine purposes)

3.2.S.6 Container-closure system

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 compendial methods (with validation) should be included, where appropriate.

For non-functional secondary packaging components (e.g. those that do not provide additional protection), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

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

Primary packaging components are those that are in direct contact with the API or FPP. The specifications for the primary packaging components should be provided and should include a specific test for identification (e.g. IR).

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 re-labelling is conducted at any stage during the API distribution process.

3.2.S.7 Stability

Refer to the Guideline on stability requirements for testing Active Pharmaceutical Ingredient (API) and Finished Pharmaceutical Products (FPP)

3.2.P Finished pharmaceutical product (FPP)

3.2.P.1 Description and Composition of the FPP

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

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

This is a list of all components of the dosage form, and their amount on a per unit basis (including overages, if any), the function of the ingredients, and a reference to their quality standards [e.g. Compendial monographs (BP, USP, JP, Ph. Eur etc) or manufacturer's specifications (IH)].

The tables in the QOS template should be used to summarize the composition of the FPP and express the quantity of each component on a per unit basis (e.g. mg per tablet, mg per ml, mg per vial) and quantity per batch. The individual ingredient for mixtures prepared in-house (e.g. coatings) should be included in the tables, where applicable.

All ingredients 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 ingredients should be declared by their proper or common names, quality standards (BP, JP, Ph.Eur, Ph.Int, USP, in-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.

Description of accompanying reconstitution diluent(s)

For FPPs supplied with reconstitution diluent(s) that have been assessed and considered acceptable (registered) in connection with another product dossier, a brief description of the reconstitution diluents(s) should be provided.

For FPPs supplied with reconstitution diluent(s) have not been assessed and considered acceptable in connection with another product dossier, the information on the diluent(s) should be provided in a separate FPP portion ("3.2.P"), as appropriate.

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

The container-closure used for the FPP (and accompanying reconstitution diluent, if applicable) should be briefly described, with further details provided under 3.2.P.7 Container-closure system, e.g. "The product is available in HDPE bottles with polypropylene caps (in sizes of 100s, 500s and 1000s) and in PVC/aluminium foil unit dose blisters (in packages of 100s) (cards of 5 × 2, 10 cards per package)."

3.2.P.2 Pharmaceutical development

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. The studies described here are distinguished from routine control tests conducted according to specifications. Additionally, this section should identify and describe the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance and FPP quality. Supportive data and results from specific studies or published literature can be included within or attached to the pharmaceutical development section. Additional supportive data can be referenced to the relevant nonclinical or clinical sections of the product dossier.

Pharmaceutical development information should include, at a minimum:

a) The definition of the quality target product profile (QTPP) as it relates to quality, safety and efficacy, considering for example the route of administration, dosage form, bioavailability, strength and stability;
b) Identification of the potential critical quality attributes (CQAs) of the FPP so as to adequately control the product characteristics that could have an impact on quality;
c) Discussion of the potential CQAs of the API(s), excipients and container-closure system(s) including the selection of the type, grade and amount to deliver drug product of the desired quality; and
d) Discussion of the selection criteria for the manufacturing process and the control strategy required to manufacture commercial lots meeting the QTPP in a consistent manner.

These features should be discussed as part of the product development using the principles of risk management over the entire life-cycle of the product.

3.2.P.2.1 Components of the FPP

3.2.P.2.1.1 Active pharmaceutical ingredient

The compatibility of the API with excipients listed in 3.2.P.1 should be discussed. Additionally, key physicochemical characteristics (e.g. water content, solubility, particle size distribution, polymorphic or solid state form)

of the API that can influence the performance of the FPP should be discussed. For fixed-dose combinations, the compatibility of APIs with each other should be discussed.

Physicochemical characteristics of the API may influence both the manufacturing capability and the performance of the FPP.

3.2.P.2.1.2 Excipients

The choice of excipients listed in 3.2.P.1, their concentration and their characteristics that can influence the FPP performance should be discussed relative to their respective functions.

3.2.P.2.2 Finished pharmaceutical product

3.2.P.2.2.1 Formulation development

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 3.2.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.

If the proposed FPP is a functionally scored tablet, a study should be undertaken to ensure the uniformity of dose in the tablet fragments. The data provided in the PD should include a description of the test method, individual values, mean and relative standard deviation (RSD) of the results. Uniformity testing (i.e. content uniformity or mass variation, depending on the requirement for the whole tablet) should be performed on each split portion from a minimum of 10 randomly selected whole tablets.

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.

The results of studies justifying the choice of in vitro dissolution or drug release conditions (e.g. apparatus, rotation speed, medium) should be provided.

Data should also be submitted to demonstrate whether the method is sensitive to changes in manufacturing processes and/or changes in grades and/or amounts of critical excipients and particle size where relevant. The dissolution method should be sensitive to any changes in the product that would result in a change in one or more of the pharmacokinetic parameters.

For slower dissolving immediate-release products (e.g. Q = 80% in 90 minutes), a second time point may be warranted (e.g. Q = 60% in 45 minutes).

Modified-release FPPs should have a meaningful in vitro release rate (dissolution) test that is used for routine quality control. Preferably this test should possess in vitro–in vivo correlation. Results demonstrating the effect of pH on the dissolution profile should be submitted if appropriate for the type of dosage form.

For extended-release FPPs, the testing conditions should be set to cover the entire time period of expected release (e.g. at least three test intervals chosen for a 12-hour release and additional test intervals for longer duration of release). One of the test points should be at the early stage of drug release (e.g. within the first hour) to demonstrate absence of dose dumping. At each test point, upper and lower limits should be set for individual units. Generally, the acceptance range at each intermediate test point should not exceed 25% or 12.5% of the targeted value. Dissolution results should be submitted for several lots, including those lots used for pharmacokinetic and bioavailability or biowaiver studies.

Recommendations for conducting and assessing comparative dissolution profiles can be found in the Guidelines on Therapeutic Equivalence Requirements.

3.2.P.2.2.2 Overages

Any overages in the formulation(s) described in 3.2.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.

3.2.P.2.2.3 Physicochemical and biological properties

Parameters relevant to the performance of the FPP, such as pH, ionic strength, dissolution, re-dispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency and/or immunological activity, should be addressed.

3.2.P.2.3 Manufacturing process development

The selection and optimization of the manufacturing process described in 3.2.P.3.3, in particular its critical aspects, should be explained. Where relevant, the method of sterilization should be explained and justified.

Where relevant, justification for the selection of aseptic processing or other sterilization methods over terminal sterilization should be provided.

Differences between the manufacturing process(es) used to produce comparative bioavailability or bio-waiver batches and the process described in 3.2.P.3.3 that can influence the performance of the product should be discussed.

The scientific rationale for the selection, optimization and scale-up of the manufacturing process described in 3.2.P.3.3 should be explained; in particular the critical aspects (e.g. rate of addition of granulating fluid, massing time, granulation end-point). A discussion of the critical process parameters (CPP), controls and robustness with respect to the QTPP and CQA of the product should be included.

3.2.P.2.4 Container-closure system

The suitability of the container-closure system (described in 3.2.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).

The suitability of the container-closure system used for the storage, transportation (shipping) and use of any intermediate/in-process products (e.g. premixes, bulk FPP) should also be discussed.

3.2.P.2.5 Microbiological attributes

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 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.

3.2.P.2.6 Compatibility

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 labelling.

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 the following paragraphs 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 labelling. These studies should preferably be conducted on aged samples. Where the labelling 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 labelling, compatibility of admixtures needs to be demonstrated only in the specified containers.

Studies should cover the duration of storage reported in the labelling (e.g. 24 hours under controlled room temperature and 72 hours under refrigeration). Where the labelling specifies co-administration with other FPPs, compatibility should be demonstrated with respect to the principal FPP as well as the co-administered FPP (i.e. in addition to other aforementioned parameters for the mixture, the assay and degradation levels of each co-administered FPP should be reported).

Refer ICH Q8 guidelines: Pharmaceutical Development for more guidance

Note: For an established non sterile generic product, a product quality review may satisfy the requirements of sections 3.2.P.2.2.1 (a), 3.2.P.2.3 (a) of the PD and QOS (See Annex VIII)

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s) (name, physical address)

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, labelling and testing should be listed. If certain companies are responsible only for specific steps

(e.g. manufacturing of an intermediate) it should be clearly indicated. 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.

A valid manufacturing authorization for pharmaceutical production, as well as a marketing authorization, should be submitted to demonstrate whether that the product is registered or licensed in accordance with national requirements. Attach a WHO-type certificate of GMP.

Regulatory situation in other countries

The countries should be listed in which this product has been granted a marketing authorization (attach evidence for marketing authorization), this product has been withdrawn from the market and/or this application for marketing has been rejected, deferred or withdrawn. (Module 1, 1.10 Regulatory Status).

3.2.P.3.2 Batch formula

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 QOS 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 ingredients 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 ingredients should be declared by their proper or common names, quality standards (e.g. BP, JP, Ph.Eur, Ph.Int, USP, house) and, if applicable, their grades (e.g. "Microcrystalline Cellulose NF (PH 102)") and special technical characteristics (e.g. lyophilized, micronized, solubilized, emulsified)

3.2.P.3.3 Description of manufacturing process and process controls

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 3.2.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 aseptic FPP, the holding time of the filtered product prior to filling should be supported by the submission of stability data, if longer than 24 hours.

Proposals for the reprocessing of materials should be justified. Any data to support this justification should be either referenced or filed in this section.

Provide a copy of the master formula and a copy of a manufacturing record for a real batch.

3.2.P.3.4 Controls of critical steps and intermediates

Critical steps: tests and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps identified in 3.2.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 and 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 or 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;
h) Parenterals: appearance, clarity, fill volume or weight, pH, filter integrity tests, particulate matter, leak testing of ampoules, pre-filtration and/or pre-sterilization bio-burden testing.

3.2.P.3.5 Process validation and/or evaluation

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).

A product quality review may be submitted in lieu of the information below.

The following information should be provided:

a) 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;
b) 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.
c) Validation information relating to the adequacy and efficacy of any sterilization process (e.g. pharmaceutical product, packaging component should be submitted.

The process validation protocol should include inter alia the following:

a) A reference to the current master production document;
b) A discussion of the critical equipment;
c) The process parameters that can affect the quality of the FPP (critical process parameters (CPPs)) including challenge experiments and failure mode operation;
d) 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);
e) 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;
f) The analytical procedures or a reference to appropriate section(s) of the dossier;
g) The methods for recording/evaluating results; and
h) 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.

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 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 extractables and lack of 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. Results on microbial contamination levels should be provided.

Note: For an established generic product a product quality review may satisfy the requirements of sections 3.2.P.3.5 of the PD and QOS **(Annex VIII).**

Refer FDA Guidance for Industry Process Validation: General Principles and Practices for more guidance at:- http://www.fda.gov/ downloads/Drugs/... /Guidances/ UCM070336. pdf

3.2.P.4 Control of excipients

3.2.P.4.1 Specifications

The specifications for excipients should be provided.

The specifications from 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 compendial 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 compendial monograph.

If the standard claimed for an excipient is a non-compendial standard (e.g. house standard) or includes tests that are supplementary to those appearing in the officially recognized compendial 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.

For oils of plant origin (e.g. soy bean, peanut) the absence of aflatoxins or biocides should be demonstrated.

The colours permitted for use are limited to those listed in the "Japanese pharmaceutical excipients", the EU "List of permitted food colours", and the 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 flavours the qualitative composition should be submitted, as well as a declaration that the excipients comply with foodstuff regulations (e.g. USA or EU).

Information that is considered confidential may be submitted directly to the PPB by the supplier with reference to the specific related product. If additional purification is undertaken on commercially available excipients details of the process of purification and modified specifications should be submitted.

3.2.P.4.2 Analytical procedures

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

3.2.P.4.3 Validation of analytical procedures

Analytical validation information, including experimental data, for the analytical procedures used for testing the excipients should be provided as in accordance to ICHQ6A.

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.

3.2.P.4.4 Justification of specifications

Justification for the proposed excipient specifications should be provided where appropriate.

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

Refer to ICHQ2A, ICHQ2B and ICHQ6A for more guidance

3.2.P.4.5 Excipients of human or animal origin

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

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.

Refer to:

- *ICH Q5A Viral safety Evaluation of Biotechnology Products derived from Cell Lines of Human or Animal Origin.*
- *ICH Q5D Quality of Biotechnological Products: Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products.*

- *Q6B Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products.*

3.2.P.4.6 Novel excipients

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 format

3.2.P.5 Control of FPP

3.2.P.5.1 Specification(s)

The specification(s) for the FPP should be provided. A copy of the FPP specification(s) from the company responsible for the batch release of the FPP should be provided. The specifications should be dated and signed by the authorized personnel (i.e. the person in charge of the quality control and quality assurance departments) should be provided in the PD. Two separate sets of specifications may be set out: after packaging of the FPP (release) and at the end of the shelf-life. Any differences between release and shelf-life tests and acceptance criteria should be clearly indicated and justified.

The specifications should be summarized according to the tables in the QOS template including the tests, acceptance criteria and analytical procedures (including types, sources and versions for the methods).

Skip testing is acceptable for parameters such as identification of colouring 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.

Refer to ICHQ3B, ICHQ3C, ICHQ6A for more guidance.

3.2.P.5.3 Validation of analytical procedures

Analytical validation information, including experimental data, for the analytical procedures used for testing the FPP should be provided.

Copies of the validation reports for the in-house analytical procedures used during pharmaceutical development (if used to support testing results provided in the MA application) as well as those proposed for routine testing should be provided.

As recognized by regulatory authorities and pharmacopoeias themselves, verification of compendial methods can be necessary. The compendial 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 compendial method(s) should be demonstrated suitable for the control of the proposed FPP.

For officially recognized compendial FPP assay methods, verification should include a demonstration of specificity, accuracy and repeatability (method precision). If an officially recognized compendial 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 compendial standard is claimed and an in-house method is used in lieu of the compendial method (e.g. for assay or for related compounds), equivalency of the in-house and compendial 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 analysed should be the placebo spiked with related compounds at concentrations equivalent to their specification limits.

Refer to ICH Q2 for more guidance.

3.2.P.5.4 Batch analyses

A description of batches and results of batch analyses should be provided.

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 should be provided for not less than three batches of at least one commercial scale batch and two pilot scale batches. Copies of the certificates of analysis for these batches should be provided and the company responsible for generating the testing results should be identified.

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).

Refer ICH Q3B, Q3C and Q6A for more guidance.

3.2.P.5.5 Characterization of impurities

Information on the characterization of impurities should be provided, if not previously provided in “3.2.S.3.2 Impurities”.

A discussion should be provided of all impurities that are potential degradation products (including those among the impurities identified in 3.2.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).

Refer ICH Q3B, Q3C and Q6A for more guidance.

3.2.P.5.6 Justification of specification(s)

Justification for the proposed FPP specification(s) should be provided.

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 compendial standard(s), etc. If the officially recognized compendial 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 marketing authorization dossier and does not need to be repeated here, although a cross-reference to their location should be provided.

3.2.P.6 Reference standards or materials

Information on the reference standards or reference materials used for testing of the FPP should be provided, if not previously provided in "3.2.S.5 Reference standards or materials".

See Section 3.2.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 3.2.S.5.

3.2.P.7 Container-closure system

A description of the container-closure systems should be provided, including the identity of materials of construction of each primary packaging component and its specification.

The specifications should include description and identification (and critical dimensions, with drawings where appropriate). Non-compendial 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 3.2.P.2.

Descriptions, materials of construction and specifications should be provided for the packaging components that are:

a) In direct contact with the dosage form (e.g. container, closure, liner, desiccant, filler);

b) Used for drug delivery (including the device(s) for multi-dose solutions, emulsions, suspensions and powders/granules for such);

c) Used as a protective barrier to help ensure stability or sterility; and

d) Necessary to ensure FPP quality during storage and shipping.

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.

Refer FDA Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics for more guidance.

3.2.P.8 Stability

The purpose of stability testing is to provide evidence of how the quality of an API or FPP varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The stability programme also includes the study of product-related factors that influence its quality, for example, interaction of API with excipients, container-closure systems and packaging materials.

3.2.P.8.1 Stability Summary and Conclusion

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.

3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment

3.2.P.8.3 Stability Data

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

Refer PPB Guidelines on Stability Requirements for Testing Active Pharmaceutical Ingredients (APIs) and Finished Pharmaceutical Products (FPPs)

3.3 REGIONAL INFORMATION

3.3.R1 Production documentation

Submit Batch Manufacturing Record (BMR) of a real batch manufactured within at most six months before the submission of the application.

MODULE 4: NON-CLINICAL STUDY REPORTS

This chapter presents the format for the organization of the nonclinical reports in the Common Technical Document for applications that will be submitted to the Pharmacy and Poisons Board.

This guidance is not intended to indicate what studies are required. It merely indicates an appropriate format for the nonclinical data that have been acquired and provide references to other guidelines which may be used for populating this format.

Generic products are generally exempted in this module. However, in some cases such as changes in safety impurity profile, the safety assessment studies should be conducted.

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 Common Technical Document.

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

Refer to

- ICH Guideline on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and marketing authorization for Pharmaceuticals (M3) for the nonclinical safety studies recommended to support human clinical trials of a given scope and duration as well as marketing authorization for pharmaceuticals.

- ICH Guideline on Safety Pharmacology Studies for Human Pharmaceuticals (S7A) for the definition, objectives and scope of safety pharmacology studies. It also addresses which studies are needed before initiation of Phase 1 clinical studies as well as information needed for marketing.
- ICH Guideline on The Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals (S7B) for a non-clinical testing strategy for assessing the potential of a test substance to delay ventricular repolarization. This Guideline includes information concerning non-clinical assays and integrated risk assessments.

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

Refer ICH Guideline on Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies (S3B) for guidance on circumstances when repeated dose tissue distribution studies should be considered (i.e., when appropriate data cannot be derived from other sources). It also gives recommendations on the conduct of such 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; including supportive toxicokinetic evaluations)

Refer to

- *ICH Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies (S3A) for guidance on developing test strategies in toxicokinetic and the need to integrate pharmacokinetics into toxicity testing, in order to aid in the interpretation of the toxicology findings and promote rational study design development.*
- *Refer The Committee for Human Medicinal Products (CHMP)Guideline on repeated dose toxicity for guidance on the conduct of repeated dose toxicity studies of active substances intended for human use.*

Refer ICH Guideline on Duration of Chronic Toxicity Testing in Animals (Rodent and Non Rodent Toxicity Testing) (S4) for the considerations that apply to chronic toxicity testing in rodents and non-rodents as part of the safety evaluation of a medicinal product. The text incorporates the guidance for repeat-dose toxicity tests.

4.2.3.3 Genotoxicity

4.2.3.3.1 In vitro
4.2.3.3.2 In vivo (including supportive toxicokinetic evaluations)

Refer to:

ICH Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use (S2) for specific guidance and recommendations for in vitro and in vivo tests and on the evaluation of test results. This document addressed two fundamental areas of genotoxicity testing: the identification of a standard set of assays to be conducted for registration, and the extent of confirmatory experimentation in any particular genotoxicity assay in the standard battery.

Refer the committee for medicinal products for human use (CHMP) guideline on the limits of genotoxic impurities for a general framework and practical approaches on how to deal with genotoxic impurities in new active substances. It also relates to new applications for existing active substances, where assessment of the route of synthesis, process control and impurity profile does not provide reasonable assurance that no new

or higher levels of genotoxic impurities are introduced as compared to products currently authorized in the EU containing the same active substance. The same also applies to variations to existing Marketing Authorizations pertaining to the synthesis.

4.2.3.4 Carcinogenicity (including supportive toxicokinetic evaluations)

Refer to:

ICH Guideline on Need for Carcinogenicity Studies of Pharmaceuticals (S1A) for a consistent definition of the circumstances under which it is necessary to undertake carcinogenicity studies on new drugs. These recommendations take into account the known risk factors as well as the intended indications and duration of exposure.

Refer ICH Guideline on Testing for Carcinogenicity of Pharmaceuticals (S1B) for guidance on the need to carry out carcinogenicity studies in both mice and rats, and guidance is also given on alternative testing procedures which may be applied without jeopardizing safety.

Refer ICH Guideline on Dose Selection for Carcinogenicity Studies of Pharmaceuticals (S1C) for the criteria for selection of the high dose for carcinogenicity studies of therapeutics. The use of other pharmacodynamic-, pharmacokinetic-, or toxicity-based endpoints in study design should be considered based on scientific rationale and individual merits.

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 toxicokinetic 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-foetal 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.

Refer to:

- *ICH Guidance on Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility (S5) for guidance on tests for reproductive toxicity. It defines the periods of treatment to be used in animals to better reflect human exposure to medical products and allow more specific identification of stages at risk.*
- *Refer committee for medicinal products for human use (CHMP) guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications for guidance on the need for, role and timing of studies in juvenile animals in the non-clinical safety evaluation of medicinal products for paediatric use.*

4.2.3.6 Local Tolerance

Refer to the Committee for medicinal products for human use (CHMP) guideline on Non-clinical local tolerance testing of medicinal products for recommendations on the evaluation of local tolerance to be performed prior to human exposure to the product. The purpose of these studies is to ascertain whether medicinal products are tolerated at sites in the body, which may come into contact with products as the result of its administration in clinical use.

4.2.3.7 Other Toxicity Studies (if available)

4.2.3.7.1 Antigenicity

4.2.3.7.2 Immunotoxicity

Refer to ICH Guideline on Immunotoxicity Studies for Human Pharmaceuticals (S8) for the recommendations on nonclinical testing for immunosuppression induced by low molecular weight drugs (non-biologicals). It applies to new pharmaceuticals intended for use in humans, as well as to marketed drug products proposed for different indications or other variations on the current product label in which the change could result in unaddressed and relevant toxicologic issues. In addition, the Guideline might also apply to drugs in which clinical signs of immunosuppression are observed during clinical trials and following approval to market.

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 toxicity studies

4.2.3.7.8 Photo safety evaluation

A harmonized guideline on photo safety evaluation of pharmaceuticals is to be published through the ICH process.

For specific products

Refer ICH Guideline on clinical Evaluation for Anticancer Pharmaceuticals (S9) for information for pharmaceuticals that are only intended to treat cancer in patients with late stage or advanced disease regardless of the route of administration, including both small molecule and biotechnology-derived pharmaceuticals. It describes the type and timing of nonclinical studies in relation to the development of anticancer pharmaceuticals and references other guidance as appropriate.

Refer ICH Guidance on Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (S6) for the pre-clinical safety testing requirements for biotechnological products. It addresses the use of animal models of disease, determination of when genotoxicity assays and carcinogenicity studies should

be performed, and the impact of antibody formation on duration of toxicology studies.

Refer committee for medicinal products for human use (CHMP) guideline on non-clinical development of fixed combinations of medicinal products for guidance on the non-clinical strategies to be considered when developing a fixed combination based on the different data available in order to support the safe human use as well as avoid unnecessary repetition of animal studies.

MODULE 5: CLINICAL STUDY REPORTS

5.1 Table of Contents of Module 5

A Table of Contents for study reports should be provided.

5.2 Tabular Listing of All Clinical Studies

5.3 Clinical Study Reports

Refer ICH Guidance on the Common Technical Document for the registration of pharmaceuticals for human use: Efficacy (M4E) for guidance on the content of this section.

Refer ICH guidelines for the structure and content of clinical study report (E3).

5.3.1 Reports of Biopharmaceutics Studies

5.3.1.1 Bioavailability (BA) Study Reports

5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports For Generic products: Refer PPB Guidelines on Therapeutic Equivalence Requirements. PART III)

5.3.1.3 In vitro-In vivo Correlation Study Reports For Generic products; Refer PPB Guidelines on Therapeutic Equivalence Requirements. PART III)

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies For Generic products; Refer PPB Guidelines on Therapeutic Equivalence Requirements. PART III)

Bioequivalence Study Requirements for Different Dosage Forms

Although this guideline concerns immediate release formulations, this section provides some general guidance on the bioequivalence data requirements for other types of formulations and for specific types of immediate release formulations.

When the test product contains a different salt, ester, ether, isomer, mixture of isomers, complex or derivative of an active substance than the comparator medicinal product, bioequivalence should be demonstrated in in vivo

bioequivalence studies. However, when the active substance in both test and comparator products is identical (or contain salts with similar properties as defined in Annex XI, Section III), in vivo bioequivalence studies may in some situations not be required as described below and in Annex IX.

Oral immediate release dosage forms with systemic action

For dosage forms such as tablets, capsules and oral suspensions, bioequivalence studies are required unless a biowaiver is applicable (see Annex XII). For oral dispersible tablets and oral solutions specific recommendations apply, as detailed below.

Oral dispersible tablets

An oral dispersible tablet (ODT) is formulated to quickly disperse in the mouth. Placement in the mouth and time of contact may be critical in cases where the active substance also is dissolved in the mouth and can be absorbed directly via the buccal mucosa. Depending on the formulation, swallowing of the e.g. coated substance and subsequent absorption from the gastrointestinal tract also will occur. If it can be demonstrated that the active substance is not absorbed in the oral cavity, but rather must be swallowed and absorbed through the gastrointestinal tract, then the product might be considered for a BCS based biowaiver (see Annex XII). If this cannot be demonstrated, bioequivalence must be evaluated in human studies.

If the ODT test product is an extension to another oral formulation, a 3-period study is recommended in order to evaluate administration of the orodispersible tablet both with and without concomitant fluid intake. However, if bioequivalence between ODT taken without water and comparator formulation with water is demonstrated in a 2-period study, bioequivalence of ODT taken with water can be assumed.

If the ODT is a generic to an approved ODT comparator medicinal product, the following recommendations regarding study design apply:

a) If the comparator medicinal product can be taken with or without water, bioequivalence should be demonstrated without water as this condition

best resembles the intended use of the formulation. This is especially important if the substance may be dissolved and partly absorbed in the oral cavity. If bioequivalence is demonstrated when taken without water, bioequivalence when taken with water can be assumed.

b) If the comparator medicinal product is taken only in one way (e.g., only with water), bioequivalence should be shown in this condition (in a conventional two-way crossover design).

c) If the comparator medicinal product is taken only in one way (e.g., only with water), and the test product is intended for additional ways of administration (e.g., without water), the conventional and the new method should be compared with the comparator in the conventional way of administration (3 treatment, 3 period, 6 sequence design).

In studies evaluating ODTs without water, it is recommended to wet the mouth by swallowing 20 ml of water directly before applying the ODT on the tongue. It is recommended not to allow fluid intake earlier than 1 hour after administration.

Other oral formulations such as oro dispersible films, buccal tablets or films, sublingual tablets and chewable tablets may be handled in a similar way as for ODTs. Bioequivalence studies should be conducted according to the recommended use of the product

5.3.2 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials

5.3.2.1 Plasma Protein Binding Study Reports

5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies

5.3.2.3 Reports of Studies Using Other Human Biomaterials

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports

5.3.3.2 Patient PK and Initial Tolerability Study Reports

5.3.3.3 Intrinsic Factor PK Study Reports

5.3.3.4 Extrinsic Factor PK Study Reports

5.3.3.5 Population PK Study Reports

5.3.4 Reports of Human Pharmacodynamic (PD) Studies

5.3.4.1 Healthy Subject PD and PK/PD Study Reports

5.3.4.2 Patient PD and PK/PD Study Reports

5.3.5 Reports of Efficacy and Safety Studies

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

5.3.5.2 Study Reports of Uncontrolled Clinical Studies

5.3.5.3 Reports of Analyses of Data from More Than One Study

5.3.5.4 Other Clinical Study Reports

5.3.6 Reports of Post-Marketing Experience if available

5.3.7 Case Report Forms and Individual Patient Listings

Refer PPB Guidelines on Therapeutic Equivalence Requirements and bio-wavers (PART III)

5.4 Literature References

Refer list of the ICH guidelines on clinical studies

ANNEXES:

Annex I – Recommended format of the Cover Letter

<Applicant>
<Address>
<Post code><Town>
<Country

<Applicant's reference> <Date>

<Pharmacy and Poisons Board>
<Address>
<Post code><Town>
<Kenya>

Dear Sir/Madam,

Subject: Submission of Application Dossier(s) for Marketing Authorization of <Product Name(s), [strength(s) of active pharmaceutical ingredient(s) and dosage form(s)

We are pleased to submit our Application Dossier(s) for a registration of human medicines which details are as follows:

Name of the medicinal product(s): ……
Pharmaceutical form(s) and strength(s): ……
INN/Active Pharmaceutical Ingredient(s): ……
ATC Code(s): ……

You will find enclosed the submission dossier as specified hereafter:

- CTD format, 2 soft copies documents format
- CD rom; Summaries in word format and body data in PDF format
- We confirm that all future submissions for this specific product will be submitted in this same format

- We confirm that the electronic submission has been checked with up-to-date and state-of-the-art antivirus software.
- The electronic submission contains the following modules:
  - Module 1: Administrative information and product information
  - Module 2: Overview and summaries
  - Module 3: Quality
  - Module 4: Non clinical study reports
  - Module 5: Clinical study reports

<The relevant fees have been paid.>

Yours sincerely,

.....

<Signature>

<Name>

<Title>

<Phone number(s)>

<Email address>

Annex II: Application Form

Application Number		
Date of submission of the dossier		
Name of the 1st Evaluator		Signature
Name of the 2nd Evaluator		Signature
Date of 1st evaluation		
Date of 2nd Evaluation		
Number of files received		
CONCLUSION OF THE ASSESSMENT **RECOMMENDED** *(no outstanding issues)* **QUERY RAISED** *(Indicate the sections where query is raised)* **REJECTED** *(indicate the module(s) that led to the rejection)* ***(Please delete which does not apply)***		
TYPE OF APPLICATION – HUMAN PRODUCT		
MODULE 1: ADMINISTRATIVE INFORMATION		
SECTION 1: PARTICULARS OF THE PRODUCT		
1.0 Name and address of Applicant		
Company name: Address: Country: Telephone: E-Mail:		
For PPB use only		
1.1	Type of the Medicinal product licence application	
	Type of the medicinal product application New/innovator MA Generic MA Conditional Authorization Emergency Use Authorization Extension application Duplicate license Renewal/Re-registration* * If variation has been made, information supporting the changes should be submitted. See PPB variation guidelines for registered medicinal products.	
1.2	Trade/Proprietary name (proprietary Product name):	

For PPB use only	
1.3	Approved / INN / generic name/Active Pharmaceutical Ingredient (API):
For PPB use only	
1.4	Strength of the Active Pharmaceutical Ingredient (API) per unit dosage of the product and specifications of the API:
For PPB use only	
1.5	Dosage form
1.5.1	Pharmaceutical Dosage form of the product:
1.5.2	Therapeutic Indication(s):
1.5.3	Route*(s)* of administration (use current list of standard terms – European Pharmacopoeia):
1.5.4	Maximum Daily Dose (MDD) for the Drug Product:
For PPB use only	
1.6	Packing/Pack size of the product:
1.6.1	Pack size:
1.6.2	Primary packing materials:
1.6.3	Secondary packing materials:
For PPB use only	
1.7	Visual Description of the product
For PPB use only	

1.8	Proposed Shelf life of the product(in months):
1.8.1	Proposed shelf life (after reconstitution or dilution):
1.8.2	Proposed shelf life (after first opening container):
1.8.3	Proposed storage conditions:
1.8.4	Proposed storage conditions after first opening:

For PPB use only	
1.9	Pharmacotherapeutic group and ATC Code
1.9.1	Pharmacotherapeutic group:

1.9.2	ATC Code:
1.9.3	If no ATC code has been assigned, please indicate if an application for ATC code has been made:
1.9.4	Proposed indication(s) for the product:
For PPB use only	
1.10	Legal category
1.10.1	Proposed dispensing category/classification:
1.10.2	For products subject to medical prescription:
1.11	Country of origin or country of release:
For PPB use only	
1.12	Product Marketing Authorisation in the country of origin. (Attach certificate of pharmaceutical product from competent regulatory authority)

☐ **Authorised** Country**:** Date of authorisation**:** Proprietary name**:** Authorisation number**:** ☐ **Refused** Country: Date of refusal (dd-mm-yyyy): Reason for Refusal:	☐ **Withdrawn** (by applicant after authorisation) Country: Date of withdrawal (dd-mm-yyyy): Proprietary name: Reason for withdrawal: ☐ **Suspended/revoked** (by competent authority) Country: Not applicable date of suspension/revocation (dd-mm-yyyy): Reason for suspension/revocation:

1.12.1	Registration status from countries with Stringent Regulatory Authorities (SRAs) where applicable
For PPB use only	
1.12.2	List of countries in which a similar application has been submitted
For PPB use only	
1.12.3	Statement on whether an application for the Marketing Authorisation has been previously rejected, withdrawn or repeatedly deferred by PPB
For PPB use only	
1.12.4	Certificates of approval of DMF (Drug Master File) by Stringent Regulatory Authority
For PPB use only	

1.12.5	Manufacturing Licence and Product Licence
For PPB use only	
1.13	**Pre-registration analysis of the finished pharmaceutical product:** (Attach certificate of analysis from a recognized WHO Prequalified Quality Control Laboratory in Kenya and within the Region)
For PPB use only	
1.14	Name(s) and complete address (es) of the manufacturer(s)
1.14.1	**Name and complete address(es)of the manufacturer(s) of the FPP, including the finished pharmaceutical product release if different from the manufacturer.**
Marketing Authorisation Holder: Company name: Address: Country: Telephone: E-Mail: **Manufactured By:** Company) Name: Address : Country :. Telephone : Telefax **:** **If the manufacturer is different to 1.1 above, explain the relationship**	
1.14.2	**Name(s) and complete address(es) of the manufacturer(s) of the active pharmaceutical ingredient**
ACTIVE INGREDIENT: Company) Name: Office Address: Country: Telephone: Fax: Contact Person : E-mail **:**	
For PPB use only	
1.15	Compliance to Good Manufacturing Practice (GMP) and Good Clinical Practice
1.15.1	Good Manufacturing Practice (GMP) from PPB
1.15.2	Good Clinical Practice (GCP) or Good Laboratory Practice (GLP)
	Information on the Reference Product (i.e., for a generic drug product application)
	Brand Name of the Reference Product:
	Dosage Form(s):
	Strength(s):
	Marketing Authorisation Holder's Name:

	Country source of Reference Product Used in Bioequivalence Study(ies):
For PPB use only	
1.16	**Name and complete address of the Local Technical Representative of Manufacture (for finished pharmaceutical Product)** Company name: Address: Country: Telephone: E-Mail: If the Local Technical Representative is different to 1.1 above, explain and provide evidence for the relationship:
For PPB use only	
1.17	Product Information
1.17.1	Summary of Product Characteristics (SPC)
1.17.2	Prescribers/Patient information leaflet:
1.17.3	Mock-ups and Photo scan of the product:
1.18	

1.18 Batch number(s) and Batch Types of the final blood product used in

Clinical/bioequivalence studies			
Stability studies			
Validation/production scale batches			

Comments: - Batch size ( )

Composition of clinical, primary stability and validation/production FPP batches ()

Ingredients	**Administration Unit**		**Bioequivalence** [batch number		**Primary stability** [batch number- **]**		**Production** [batch number**]**	
	Mg/ IU	%*	Kg	%*	Kg	%*	kg	%*
Active :								
Excipients:								

	Equivalence of the composition or justified differences	The compositions of the stability and validation batches are the same and differences are justified.
1.19	State the reference/monograph standard such as British Pharmacopeia, United States Pharmacopeia, Ph. Eur, Japanese Pharmacopeia, In-house monograph e.t.c. used for Finished Medicinal Product.	
1.19.1	Specification of active ingredient(s) from API manufacturer (Specification number and Version):	
1.19.2	Specification of active ingredient(s) from FPP manufacturer (Specification number and Version):	
1.19.3	Specification of Finished Pharmaceutical Product (Specification number and Version):	
1.20	Name and address (physical and postal) of the Contract Research Organisation(s) where the clinical studies of the product were conducted. *(If applicable)* Company name: Address: Country: Telephone: Telefax: E-Mail:	

1.21 DECLARATION BY AN APPLICANT
I, the undersigned certify that all the information in this form and accompanying documentation is correct, complete and true to the best of my knowledge. I further confirm that the information referred to in my application dossier is available for verification during GMP inspection. I also agree that I shall carry out pharmacovigelance to monitor the safety of the product in the market and provide safety update reports to the National Medicines Regulatory Authority. I further agree that I am obliged to follow the requirements of Kenya, and Legislations and Regulations which are applicable to medicinal products. Name: Position in the company: Signature: Date: For PPB use only OVERALL QUERIES AND RECOMMENDATIONS FOR THIS MODULE Official stamp: ..... ** Note: If fees have been paid, attach proof of payment*

PPB use only

Annex III: Expert Declaration Form

The following is an example of a suitable declaration form:

Quality /Non-clinical / Clinical (delete those not appropriate)

I, the undersigned, declare that I have:

i. the suitable technical or professional qualifications to act in this capacity (for more information, refer to the enclosed *curriculum* vitae).

ii. fully examined the data provided by the applicant and have provided references to the literature to support statements made that are not supported by the applicant's original data. This report presents an objective assessment of the nature and extent of the data.

iii. provided a report based on my independent assessment of the data provided.

iv. based my recommendations, regarding suitability for registration, on the data provided herewith. I have considered the attached data and have recommended as to suitability for registration of the intended dose forms and presentations according to the proposed product information document.

v. I further declare that this expert report represents my own view.

vi. Further, I declare the following to be the full extent of the professional relationship between myself and the applicant:

.....

.....

.....

.....

Annex IV: Quality Information Summary (QIS)

< Add Dossier Application number>

BACKGROUND:

The PPB Quality Information Summary model is adopted from the WHO QIS template of 12th July 2017.

QUALITY INFORMATION SUMMARY (QIS)

INTRODUCTION

a) Summary of product information:

Non-proprietary name(s) of the finished pharmaceutical product(s) (FPP)	
Proprietary name(s) of the finished pharmaceutical product(s) (FPP)	
International non-proprietary name(s) of the active pharmaceutical ingredient(s) (API(s)), including form (salt, hydrate, polymorph)	
Applicant name and address	
Dosage form	
Application Number	
Strength	
Route of administration	
Proposed indication(s)	
Local Technical Representative (Agency)	
LTR Contact person details	
Local Technical Representative (LTR) contact person	
Physical address details	
Town/City	
Postal code	
Country (Within Kenya)	
Contact person's email address	
Contact person's phone number	
FPP manufacturer Qualified Person	
FPP manufacturer Qualified person's contact details (including Physical address)	
Unit /block	
Road/Street	
Plant	
Village/suburb	
Town/City	
Postal code	

Country	
Contact person's email address	
Contact person's phone number	

b) Administrative Summary:

Applicant's date of preparation or revision of the QIS	
Version and/or date of acceptance	*(PPB use only)*

Related dossiers (e.g. FPP(s) with the same API(s) submitted to PPB by the applicant):

Application number ( )	Registered (Y/N)	API, strength, dosage form (eg. Irinotecan (as chloride) 20mg per ml Solution)	API manufacturer (including address if same manufacturer as current dossier)

2.3.S DRUG SUBSTANCE (or ACTIVE PHARMACEUTICAL INGREDIENT (API)) (NAME, MANUFACTURER)

Indicate which option applies for the submission of API information: <check one only>

Name of API:	
Name of API manufacturer:	
□	Certificate of suitability to the European Pharmacopoeia (CEP) Option 1.
□	Confirmation of API prequalification document: Option 2
□	API Ref No; _____. Option 3a.
□	PPB Active pharmaceutical ingredient master file (PPB APIMF) procedure: APIMF number assigned by PPB (if known): _____ ; version number(s) including amendments (and/or date(s)) of the open part: _____ ; version number(s) including amendments (and/or date(s)) of the restricted part: : _____. Option 3b.

□	Full details in the PD Open part DMF version number_____ Restricted part DMF version number_____ Identifier of current module 3.2.S: _____ Option 4.

2.3.S.2 Manufacture (name, manufacturer)

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

a) Name, address and responsibility (e.g. fabrication, packaging, labelling, testing, storage) of each manufacturer, including contractors and each proposed production site or facility involved in these activities:

Name and address (including block(s)/unit(s))	Responsibility	CEP number/ WHOAPI-PQ number /WHO APIMF/ PPB registration No./PPB APIMF/ if applicable)	Letter of access provided?

2.3.S.2.3 Control of Materials (name, manufacturer) – <u>for API option 4 only</u>

a) Name of starting material:

b) Name and manufacturing site address of starting material manufacturer(s):

2.3.S.4 Control of the API (name, manufacturer)

2.3.S.4.1 Specification (name, manufacturer)

API specifications of the FPP manufacturer:

Standard (e.g. Ph.Int., Ph.Eur., BP, USP, in-house)	
Specification reference number & version effective date	

Test	Acceptance criteria	Analytical procedure (Type/Source/Version)
Description		
Identification		
Impurities		
Assay		
etc.		

2.3.S.6 Container Closure System (name, manufacturer)

a) Description of the container closure system(s) for the storage and shipment of the API:

2.3.S.7 Stability (name, manufacturer)

2.3.S.7.1 Stability Summary and Conclusions (name, manufacturer)

c) Proposed storage conditions and re-test period (or shelf-life, as appropriate):

Container closure system	Storage statement	Re-test period*

* indicate if a shelf-life is proposed in lieu of a re-test period (e.g. in the case of labile APIs)

2.3.P DRUG PRODUCT (or FINISHED PHARMACEUTICAL PRODUCT (FPP))

Indicate which option applies for the submission of FPP information: <check one only>

Name of API:	
Name of API manufacturer:	
▪	Full details

▪	WHO collaborative procedure
▪	SRA Abridged procedure
▪	PPB Mutual Recognition
▪	EU Article 58 procedure

2.3.P.1 Description and Composition of the FPP

a) Description of the FPP (in signed specifications):

b) Composition of the FPP:

i. Composition, i.e. list of all components of the FPP and their amounts on a per unit basis and percentage basis (including individual components of mixtures prepared in-house (e.g. coatings) and overages, if any):

Component and quality standard (and grade, if applicable)	**Function**	**Strength (label claim)**					
		Quant. per unit or per mL	**%**	**Quant. per unit or per mL**	**%**	**Quantity per unit or per mL**	**%**
<complete with appropriate titles e.g. Core tablet (Layer 1, Layer 2, etc. as applicable), Contents of capsule, Powder for injection>							
Subtotal 1							
<complete with appropriate title e.g. Film-coating >							
Subtotal 2							
Total							

ii. **Composition of all *components purchased as mixtures* (e.g. colorants, coatings, capsule shells, imprinting inks):**

Description of accompanying reconstitution diluent(s), if applicable:

2.3.P.2.2.1 Formulation Development

c) Information on primary (submission, registration, exhibit) batches including comparative bioavailability or biowaiver, stability, commercial:

Batch number(s) of the FPPs used in			
Bioequivalence	<e.g. bioeq. batch A12345>.		
Biowaiver	<e.g. biowaiver batch X12345>		
For proportional strength biowaiver: the bioequivalence batch of the reference strength			
Dissolution profile studies			
Stability studies (primary batches)			
‹Packaging configuration I›			
‹ packaging configuration II›			
‹Add/ delete as many rows as necessary›			
Stability studies (production batches)			
‹ Packaging configuration I›			
‹ Packaging configuration II›			
(Add/ delete as many rows as necessary)			
Validation studies (primary batches)			
‹ Packaging configuration I›			
‹ Packaging configuration II›			
(Add/ delete as many rows as necessary)			
Validation studies (at least the first three consecutive production batches) version(s) for process validation protocol(s)			

Summary of batch numbers:

Summary of formulations and discussion of any differences:

Component and quality standard (e.g. NF, BP, Ph.Eur, in-house)	**Relevant batches**							
	Comparative bioavailability or biowaiver		**Stability**		**Process validation**		**Commercial (2.3.P.1)**	
	<Batch nos. and sizes>		**<Batch nos. and sizes>**		**<Batch nos. and sizes>**		**<Batch nos. and sizes>**	
	Theor. quantity per batch	**%**	**Theor. quantity per batch**	**%**	**Theor. quantity per batch**	**%**	**Theor. quantity per batch**	**%**
<complete with appropriate titles e.g. Core tablet (Layer 1, Layer 2, etc. as applicable), Contents of capsule, Powder for injection>								
Subtotal 1								
<complete with appropriate title e.g. Film-coating >								

Component and quality standard (e.g. NF, BP, Ph.Eur, in-house)	Relevant batches							
	Comparative bioavailability or biowaiver		Stability		Process validation		Commercial (2.3.P.1)	
	<Batch nos. and sizes>		<Batch nos. and sizes>		<Batch nos. and sizes>		<Batch nos. and sizes>	
	Theor. quantity per batch	%	Theor. quantity per batch	%	Theor. quantity per batch	%	Theor. quantity per batch	%
Subtotal 2								
Total								

2.3.P.3 Manufacture

2.3.P.3.1 Manufacturer(s)

a) Name, address and responsibility (e.g. fabrication, packaging, labelling, testing) of each manufacturer, including contractors and each proposed production site or facility involved in manufacturing and testing:

Name and address (include block(s)/unit(s))	Name and address (include block(s)/unit(s))

2.3.P.3.2 Batch Formula

Largest intended commercial batch size:

Other intended commercial batch sizes:

<information on all intended commercial batch sizes should be in the QIS>

a) List of all components of the FPP to be used in the manufacturing process and their amounts on a per batch basis (including

components of mixtures prepared in-house (e.g. coatings) and overages, if any):

Strength (label claim)			
Master production document reference number and/or version			
Proposed commercial batch size(s) (e.g. number of dosage units)			
Component and quality standard (and grade, if applicable)	**Quantity per batch (e.g. kg/batch)**	**Quantity per batch (e.g. kg/batch)**	**Quantity per batch (e.g. kg/batch)**
<complete with appropriate titles e.g. Core tablet (Layer 1, Layer 2, etc. as applicable), Contents of capsule, Powder for injection>			
Subtotal 1			
<complete with appropriate title e.g. Film-coating >			
Subtotal 2			
Total			

2.3.P.3.3 Description of Manufacturing Process and Process Controls

a) Flow diagram of the manufacturing process:

b) Narrative description of the manufacturing process, including equipment type and working capacity, process parameters:

2.3.P.3.4 Controls of Critical Steps and Intermediates

a) **Summary of controls performed at the critical steps of the manufacturing process and on isolated intermediates:**

Step (e.g. granulation, compression, coating)	Controls (parameters/limits/frequency of testing)

Proposed/validated holding periods for intermediates (including bulk product):

a) Summary of the process validation and/or evaluation studies conducted and/or a summary of the proposed validation protocol for the critical steps or critical assays used in the manufacturing process (e.g. protocol number, parameters, results):

Document code(s) for the process validation protocol(s) and/or report(s) (including reference number/version/date):

2.3.P.5 Control of FPP

2.3.P.5.1 Specification(s)

a) Specification(s) for the FPP:

Standard (e.g. Ph.Int., BP, USP, in-house)			
Specification reference number and version			
Test	**Acceptance criteria (release)**	**Acceptance criteria (shelf-life)**	**Analytical procedure (type/source/version)**
Description			
Identification			
Impurities			
Assay			
etc.			

2.3.P.7 Container Closure System

a) Description of the container closure systems, including unit count or fill size, container size or volume:

Description (including materials of construction)	**Strength**	**Unit count or fill size (e.g. 60s, 100s etc.)**	**Container size (e.g. 5 ml, 100 ml etc.)**

2.3.P.8 Stability

2.3.P.8.1 Stability Summary and Conclusions

b) Proposed storage statement and shelf-life (and in-use storage conditions and in-use period, if applicable):

Container closure system	Storage statement	Shelf-life

2.3.P.8.2 Post-approval Stability Protocol and Stability Commitment

a) Stability protocol for Primary stability batches (e.g. storage conditions (including tolerances), batch numbers and batch sizes, tests and acceptance criteria, testing frequency, container closure system(s)):

Parameter	**Details**	
Storage condition(s) (◦C, % RH)		
Batch number(s) / batch size(s)	<*primary batches*>	
Tests and acceptance criteria	Description	
	Moisture	
	Impurities	
	Assay	
	etc.	
Testing frequency		
Container closure system(s)		

Parameter	Details

b) Stability protocol for Commitment batches (e.g. storage conditions (including tolerances), batch numbers (if known) and batch sizes, tests and acceptance criteria, testing frequency, container closure system(s)):

Parameter	Details	
Storage condition(s) (◦C, % RH)		
Batch number(s) / batch size(s)	*<not less than three production batches in each container closure system>*	
Tests and acceptance criteria	Description	
	Moisture	
	Impurities	
	Assay	
	etc.	
Testing frequency		
Container closure system(s)		

c) Stability protocol for Ongoing Batches (e.g. storage conditions (including tolerances), number of batches per strength and batch sizes, tests and acceptance criteria, testing frequency, container closure system(s)):

Parameter	Details
Storage condition(s) (◦C, % RH)	

Parameter	Details	
Batch size(s), annual allocation	*<at least one production batch per year (unless none is produced that year) in each container closure system >*	
Tests and acceptance criteria	Description	
	Moisture	
	Impurities	
	Assay	
	etc.	
Testing frequency		
Container closure system(s)		

2.3.P.8.3 Stability Data

d) Bracketing and matrixing design for commitment and/or continuing (i.e. ongoing) batches, if applicable:

WRITTEN COMMITMENTS OF THE MANUFACTURER – for PPB use

API

If applicable (primary stability study commitment):

The Applicant (or API manufacturer) undertook in writing (date of letter of commitment) to continue long-term testing of <INN of API> for a period of time sufficient to cover the whole provisional re-test period (period ending month/year) and to report any significant changes or out-of-specification results immediately to PPB for the following batches :

<Batch numbers, manufacturing dates, batch size, primary packing materials>

If applicable (commitment stability studies):

Since stability data on three production scale batches were not provided with the application, the remaining number of production scale batches should be put on long-term stability testing. Any significant changes or out-of-

specification results should be reported immediately to PPB. The approved stability protocol should be used for commitment batches.

API option 1 – CEP

The Applicant provided a commitment in writing (date of letter of commitment) to inform PPB in the event that the CEP is revised or withdrawn, and that revisions to the CEP will be handled as per variation PPB Variation guidelines. Note that revisions or withdrawal will require additional consideration of the API data requirements to support the dossier.

API option 2 – WHOAPI-CPQ

The Applicant provided a commitment in writing (date of letter of commitment) to inform PPB in the event that the WHOAPI-CPQ is revised or withdrawn, and that revisions to the WHOAPI-CPQ will be handled as per variation PPB Variation guidelines. Note that revisions or withdrawal will require additional consideration of the API data requirements to support the dossier.

API option 4 – full details in the PD (ongoing stability study commitment)

The Applicant undertook in writing (date of letter of commitment) a commitment regarding ongoing stability studies. Unless otherwise justified, at least one batch per year of the product will be included in the stability programme (unless none is produced during that year). The stability protocol will be that which was approved for primary batches (or the protocol was submitted for assessment). Out-of-specification results or significant atypical trends will be investigated. Any confirmed significant change or out-of-specification result will be reported immediately to PPB. The possible impact on batches on the market will be considered in consultation with PPB-EWG GMP inspection.

FPP

If applicable (primary stability study commitment):

The Applicant undertook in writing (date of letter of commitment) to continue long-term testing of < FPP reference number, trade name (INN of API), strength, pharmaceutical form> for a period of time sufficient to cover the whole provisional shelf-life (period ending month/year) and to report any out-of-specification results or significant changes immediately to PPB for the following batches:
<Batch numbers, manufacturing dates, batch size, primary packing materials >

If applicable (commitment stability studies):

Since stability data on three production scale batches was not provided with the application, the Applicant undertook in writing, (date of letter of commitment) to put the remaining number <e.g. additional two (2)> production scale batches of < FPP reference number, trade name (INN of API), strength, pharmaceutical form, primary packing material> on long-term stability testing. Any out-of-specification results or significant changes during the study will immediately be reported to PPB. The approved stability protocol will be used for commitment batches.

If applicable (when the proposed largest commercial batch size is 200 000 units (x units) or less)

The Applicant undertook in writing (date of letter of commitment) to place the first three batches of any production size larger than x units on stability. The stability protocol will be that which was approved for primary batches (or the protocol was submitted for assessment). Out-of-specification results or significant atypical trends will be investigated. Any confirmed significant change or out-of-specification result will be reported immediately to PPB.

Ongoing stability study commitment

The Applicant undertook in writing (date of letter of commitment) a commitment regarding ongoing stability studies. Unless otherwise justified, at least one batch per year of the product manufactured in every primary packaging type will be included in the stability programme (unless none is produced during that year). The stability protocol will be that which was approved for primary batches (or the protocol was submitted and found acceptable). Out-of-specification results or significant atypical trends will be investigated. Any confirmed significant change or out-of-specification result will be reported immediately to PPB. The possible impact on batches on the market will be considered in consultation with PPB GMP inspection.

If applicable (validation of production batches)

Validation data on production scale batches of not less than three (3) consecutive batches of <FPP reference number, trade name (INN of API), strength, pharmaceutical form, primary packing material> was not provided with the application. Therefore, the Applicant submitted a written commitment (date of letter of commitment) that three consecutive production batches would be prospectively validated and a validation report —in accordance with the details of the validation protocol provided in the dossier— would be made available as soon as possible for evaluation by assessors or for verification by the PPB GMP inspection.

Change History

Date of preparation of original QIS:

Date of revised version	Section (e.g. S.2.1)	Revision

Annex V: Letter of Access to CEP

<Applicant>
<Address>
<Post code><Town>
<Country

<Applicant's reference> <Date>

The Pharmacy and Poisons Board
P. O. Box 27663 - 00506
Lenana Road, Nairobi,
Kenya

Dear Sir/Madam,

Subject: Authorization to access Certificate of Suitability (CEP)

Reference is made to the above subject matter.

Consent is hereby granted to (*Name PPB*) to make reference to this company's Certificate(s) of Suitability (CEPs) [*number(s)*] for [*API(s) name(s)*] in the evaluation of applications relating to the registration of [*medicine name(s)*] submitted to (*name of PPB-PPB*) by (*applicant's name*).

This consent does/does not** include authorization to supply information or extracts from or the whole of the data to:

(Name of company or individual)

The API is manufactured by:
(*Names and addresses of all manufacturing sites and manufacturing steps carried out at site*)

A formal agreement exists between the applicant of the medicine and the manufacturer of the API which ensures that information will be communicated between them and to PPB before any significant change is made to the site of manufacture, manufacturing procedure or quality control

specifications of the API. Except as permitted by the PPB guidelines relating to changes to medicines, such changes will not be made to the API to be used in manufacture of the medicine destined to be distributed in Kenya before written approval is granted by the PPB.

I understand that the consequences of failure to obtain approval for changes where approval is necessary may include de-registration and recall of batches of medicines.

Any questions arising from the PPB's evaluation of this CEP should be forwarded to: (*Name and address*)

Yours faithfully

{Signature of Company Representative}
{Name}
{Position in Company}
{Date}

Annex VI: Letter of Access to EAC-APIMF

<Applicant>
<Address>
<Post code><Town>
<Country

<Applicant's reference> <Date>

The Pharmacy and Poisons Board
P. O. Box 27663 - 00506
Lenana Road, Nairobi,
Kenya

Dear Sir/Madam,

Subject: Authorization to access Active Pharmaceutical Ingredient Master File

Reference is made to the above subject matter.

Consent is hereby granted to (*Name of Manufacturer*) to make reference to this company's Active Pharmaceutical Ingredient Master File(s) for [API(s) name] in the evaluation of applications relating to the registration of [medicine name(s)] submitted to (*PPB*) by the (applicant's name).

This consent does/does not** include authorization to supply information or extracts from or the whole of the data to:

(Name of company or individual)

The substance is manufactured by:

(Names and addresses of all manufacturing sites and manufacturing steps carried out at site)

A copy of the *applicant's Part of the APIMF* as specified in the EAC Active Pharmaceutical Ingredient Master File Procedure has been supplied to the applicant.

A formal agreement exists between the applicant of the medicine and the manufacturer of the API which ensures that information will be communicated between them and to PPB before any significant change is made to the site of manufacture, manufacturing procedure or quality control specifications of the API. Except as permitted by the PPB guidelines relating to changes to medicines, such changes will not be made to the API to be used in manufacture of the medicine destined to be distributed in Kenya before written approval is granted by the PPB.

I understand that the consequences of failure to obtain approval for changes where approval is necessary may include de-registration and recall of batches of medicines.

This APIMF (or data identical to that contained therein) has also been submitted to and approved by the regulatory authorities in (*list of countries with stringent regulatory systems*), and the [*name(s) of PPB NMR(s)*] is authorized to request and refer to the evaluation reports of these agencies. *PPB* is also authorized to exchange its own evaluation reports with these and other regulatory authorities.

Any questions arising from the evaluation of this APIMF should be forwarded to:

{Name and address}

Yours faithfully

{Signature of Company Representative}
{Name}
{Position in Company}
{Date}

Annex VII: Quality Overall Summary – Product Dossier (QOS- PD)

Summary of product information:

Non-proprietary name of the finished pharmaceutical product (FPP)			
Proprietary name of the finished pharmaceutical product (FPP)			
International non-proprietary name(s) of the active pharmaceutical ingredient(s) (API(s)), including form (salt, hydrate, polymorph)			
Applicant name and address			
Dosage form			
Reference Number(s)			
Strength(s)			
Route of administration			
Proposed indication(s)			
Contact information	Name: Phone: Fax: Email:		

2.3.S ACTIVE PHARMACEUTICAL INGREDIENT (API))

Complete the following table for the option that applies for the submission of API information:

Name of API:	
Name of API manufacturer:	

□	Certificate of suitability to the European Pharmacopoeia (CEP): is a written commitment provided that the applicant will inform PPB in the event that the CEP is withdrawn and has acknowledged that withdrawal of the CEP will require additional consideration of the API data requirements to support the dossier: □ yes, □ no; a copy of the most current CEP (with annexes) and written commitment should be provided in *Module 1*; the declaration of access should be filled out by the CEP holder on behalf of the FPP manufacturer or applicant to the PPB who refers to the CEP; and summaries of the relevant information should be provided under the appropriate sections (e.g. S.1.3, S.3.1, S.4.1 through S.4.4, S.6 and S.7; see Quality guideline).

□	Active pharmaceutical ingredient master file (APIMF): A copy of the letter of access should be provided in *Module 1*; and summaries of the relevant information from the Open part should be provided under the appropriate sections; see Section 3.2.S in the Quality guideline.
□	Active pharmaceutical ingredient pre-qualified by WHO Provide evidence from WHO
□	Full details in the PD: Summaries of the full information should be provided under the appropriate sections; see Section 3.2.S in the Quality guideline.

2.3.S.1 General Information

2.3.S.1.1 Nomenclature

a) (Recommended) International Non-proprietary name (INN):
b) Compendial name, if relevant:
c) Chemical name(s):
d) Company or laboratory code:
e) Other non-proprietary name(s) (e.g. national name, USAN, BAN):
f) Chemical Abstracts Service (CAS) registry number:

2.3.S.1.2 Structure

a) Structural formula, including relative and absolute stereochemistry:
b) Molecular formula:
c) Relative molecular mass:

2.3.S.1.3 General Properties

a. Physical description (e.g. appearance, colour, physical state):
b. Solubilities:

In common solvents:

Quantitative aqueous pH solubility profile (pH 1 to 6.8):

Medium (e.g. pH 4.5 buffer)	**Solubility (mg/ml)**

Dose/solubility volume calculation:

c. Physical form (e.g. polymorphic form(s), solvate, hydrate):

Polymorphic form:

Solvate:

Hydrate:

d. Other:

Property	
pH	
pK	
Partition coefficients	
Melting/boiling points	
Specific optical rotation (specify solvent)	
Refractive index (liquids)	
Hygroscopicity	
UV absorption maxima/molar absorptivity	
Other	

2.3.S.2 Manufacture

2.3.S.2.1 Manufacturer(s)

a) Name, address and responsibility (e.g. fabrication, packaging, labelling, testing, storage) of each manufacturer, including contractors and each proposed production site or facility involved in these activities:

b) Manufacturing authorization for the production of API(s) and, where available, certificate of GMP compliance (GMP information should be provided in Module 1):

2.3.S.2.2 Description of Manufacturing Process and Process Controls

a) Flow diagram of the synthesis process(es):

b) Brief narrative description of the manufacturing process(es):

c) Alternate processes and explanation of their use:

d) Reprocessing steps and justification:

2.3.S.2.3 Control of Materials

(a) Summary of the quality and controls of the starting materials used in the manufacture of the API:

Step/starting material	Test(s)/method(s)	Acceptance criteria

(b) Name and manufacturing site address of starting material manufacturer(s):

(c) Where the API(s) and the starting materials and reagents used to manufacture the API(s) are without risk of transmitting agents of animal spongiform encephalopathies, a letter of attestation confirming this can be found in:

2.3.S.2.4 Controls of Critical Steps and Intermediates

(a) Summary of the controls performed at critical steps of the manufacturing process and on intermediates:

Step/materials	Test(s)/method(s)	Acceptance criteria

2.3.S.2.5 Process Validation and/or Evaluation

(a) Description of process validation and/or evaluation studies (e.g. for aseptic processing and sterilization):

2.3.S.2.6 Manufacturing Process Development

(a) Description and discussion of the significant changes made to the manufacturing process and/or manufacturing site of the API used in producing comparative bioavailability or bio-waiver, stability, scale-up, pilot and, if available, production scale batches:

2.3.S.3 Characterisation

2.3.S.3.1 Elucidation of Structure and other Characteristics

a) List of studies performed (e.g. IR, UV, NMR, MS, elemental analysis) and conclusion from the studies (e.g. whether results support the proposed structure):

b) Discussion on the potential for isomerism and identification of stereochemistry (e.g. geometric isomerism, number of chiral centres and configurations) of the API batch(es) used in comparative bioavailability or biowaiver studies:

c) Summary of studies performed to identify potential polymorphic forms (including solvates):

d) Summary of studies performed to identify the particle size distribution of the API:

e) Other characteristics:

2.3.S.3.2 Impurities

a) Identification of potential and actual impurities arising from the synthesis, manufacture and/or degradation:

i. List of API-related impurities (e.g. starting materials, by-products, intermediates, chiral impurities, degradation products), including chemical name, structure and origin:

API-related impurity (chemical name or descriptor)	Structure	Origin

ii. List of process-related impurities (e.g. residual solvents, reagents), including compound names and step used in synthesis:

Process-related impurity (compound name)	Step used in synthesis

b) Basis for setting the acceptance criteria for impurities:

i. Maximum daily dose (i.e. the amount of API administered per day) for the API, corresponding to ICH Reporting/Identification/Qualification Thresholds for the API-related impurities and the concentration limits (ppm) for the process-related impurities (e.g. residual solvents):

Maximum daily dose for the API:	**<x mg/day>**	
Test	**Parameter**	**ICH threshold or concentration limit**
API-related impurities	Reporting Threshold	
	Identification Threshold	
	Qualification Threshold	
Process-related impurities	<solvent 1>	
	<solvent 2>, etc.	

ii. Data on observed impurities for relevant batches (e.g. comparative bioavailability or bio-waiver studies, stability

Impurity (API-related and process-related)	**Acceptance Criteria**	**Results (include batch number* and use**)**		

include strength, if reporting impurity levels found in the FPP (e.g. for comparative studies) e.g. comparative bioavailability or bio-waiver studies, stability

iii. Justification of proposed acceptance criteria for impurities:

2.3.S.4 Control of the API

2.3.S.4.1 Specification

a) API specifications *of the FPP manufacturer*:

Standard (e.g. Ph.Int., Ph.Eur., BP, USP, House)		
Specification reference number and version		
Test	**Acceptance criteria**	**Analytical procedure (Type/Source/Version)**
Description		
Identification		
Impurities		
Assay		
etc.		

2.3.S.4.2 Analytical Procedures

a) Summary of the analytical procedures (e.g. key method parameters, conditions, system suitability testing):

2.3.S.4.3 Validation of Analytical Procedures

a) Summary of the validation information (e.g. validation parameters and results for non-compendia methods):

b) Summary of verification information on compendia methods

2.3.S.4.4 Batch Analyses

a) Description of the batches:

Batch number	**Batch size**	**Date and site of production**	**Use (e.g. comparative bioavailability or biowaiver, stability)**

b) Summary of batch analyses release results of the FPP manufacturer for relevant batches (e.g. comparative bioavailability or bio-waiver, stability):

Test	**Acceptance Criteria**	**Results**		
		<batch x>	**<batch y>**	**etc.**
Description				
Identification				
Impurities				
Assay				
etc.				

c) Summary of analytical procedures and validation information for those procedures not previously summarized in 2.3.S.4.2 and 2.3.S.4.3 (e.g. historical analytical procedures):

2.3.S.4.5 Justification of Specification

a) Justification of the API specification (e.g. evolution of tests, analytical procedures and acceptance criteria, differences from officially recognized compendial standard(s)):

2.3.S.5 Reference Standards or Materials

(a) Source (including lot number) of primary reference standards or reference materials (e.g. Ph.Int., Ph.Eur., BP, USP, in-house):

(b) Characterization and evaluation of non-official (e.g. not from an officially recognized pharmacopoeia) primary reference standards or reference materials (e.g. elucidation of structure, certificate of analysis):

(c) Description of the process controls of the secondary reference standard (comparative certificate of analysis and IR spectra against primary standard)

:

2.3.S.6 Container Closure System

(a) Description of the container closure system(s) for the shipment and storage of the API (including the identity of materials of construction of each primary packaging component and a brief summary of the specifications):

Packaging component	**Materials of construction**	**Specifications (list parameters e.g. identification (IR))**

(b) Other information on the container closure system(s) (e.g. suitability studies):

2.3.S.7 Stability

2.3.S.7.1 Stability Summary and Conclusions

(a) Summary of stress testing (e.g. heat, humidity, oxidation, photolysis, and acid/base): and results:

Stress condition	**Treatment**	**Results (e.g. including discussion whether mass balance is observed)**
Heat		
Humidity		
Oxidation		
Photolysis		
Acid		
Base		
Other		

(b) Summary of accelerated and long-term testing parameters (e.g. studies conducted):

Storage condition (◦C, % RH)	**Batch number**	**Batch size**	**Container closure system**	**Completed (and proposed) testing intervals**

Summary of the stability results observed for the above accelerated and long-term studies:

Test	**Results**
Description	

Test	Results
Moisture	
Impurities	
Assay	
etc.	

* indicate if a shelf-life is proposed in lieu of a re-test period (e.g. in the case of labile APIs)

2.3.S.7.2 Post-approval Stability Protocol and Stability Commitment

a) Stability protocol for Primary stability batches (e.g. storage conditions (including tolerances), batch numbers and batch sizes, tests and acceptance criteria, testing frequency, container closure system(s)):

Parameter	Details	
Storage condition(s) (◦C, % RH)		
Batch number(s) / batch size(s)		
Tests and acceptance criteria	Description	
	Moisture	
	Impurities	
	Assay	
	etc.	
Testing frequency		
Container closure system(s)		

b) Stability protocol for Commitment batches (e.g. storage conditions (including tolerances), batch numbers (if known) and batch sizes, tests and acceptance criteria, testing frequency, container closure system(s)):

Parameter	Details
Storage condition(s) (◦C, % RH)	
Batch number(s) / batch size(s)	*<not less than three production batches>*

Parameter	Details	
Tests and acceptance criteria	Description	
	Moisture	
	Impurities	
	Assay	
	etc.	
Testing frequency		
Container closure system(s)		

c) Stability protocol for Ongoing batches (e.g. storage conditions (including tolerances), batch sizes and annual allocation, tests and acceptance criteria, testing frequency, container closure system(s)):

Parameter	Details	
Storage condition(s) (◦C, % RH)		
Annual allocation	*<at least one production batch per year (unless none is produced that year) in each container closure system >*	
Tests and acceptance criteria	Description	
	Moisture	
	Impurities	
	Assay	
	etc.	
Testing frequency		
Container closure system(s)		

2.3.S.7.3 Stability Data

a) The actual stability results should be provided in Module 3.

b) Summary of analytical procedures and validation information for those procedures not previously summarized in 2.3.S.4 (e.g. analytical procedures used only for stability studies):

2.3.P FINISHED PHARMACEUTICAL PRODUCT (FPP))

2.3.P.1 Description and Composition of the FPP

a) Description of the FPP:

b) Composition of the FPP:

i. Composition, i.e. list of all components of the FPP and their amounts on a per unit basis and percentage basis (including individual components of mixtures prepared in-house (e.g. coatings) and overages, if any):

Component and quality standard (and grade, if applicable)	**Function**	**Strength (label claim)**					
		Quant. per unit	**%**	**Quant. per unit**	**%**	**Quantity per unit**	**%**
<complete with appropriate title e.g. Core tablet, Contents of capsule, Powder for injection>							
Subtotal 1							
<complete with appropriate title e.g. Film-coating>							
Subtotal 2							
Total							

ii. Composition of all components purchased as mixtures (e.g. colourants, coatings, capsule shells, imprinting inks):

c) Description of accompanying reconstitution diluent(s), if applicable:

d) Type of container closure system used for the FPP and accompanying reconstitution diluent, if applicable:

2.3.P.2 Pharmaceutical Development

2.3.P.2.1 Components of the FPP

2.3.P.2.1.1 Active Pharmaceutical Ingredient

a) Discussion of the:

i. Compatibility of the API(s) with excipients listed in 2.3.P.1

ii. Key physicochemical characteristics (e.g., water content, solubility, particle size distribution, polymorphic or solid-state form) of the API(s) that can influence the performance of the FPP:

iii. For fixed-dose combinations, compatibility of APIs with each other:

2.3.P.2.1.2 Excipients

a) Discussion of the choice of excipients listed in 2.3.P.1 (e.g. their concentrations, their characteristics that can influence the FPP performance):

2.3.P.2.2 Finished Pharmaceutical Product

2.3.P.2.2.1 Formulation Development

a) Summary describing the development of the FPP (e.g. route of administration, usage, optimization of the formulation, etc.):
b) Information on primary (submission, registration, exhibit) batches including comparative bioavailability or bio-waiver, stability, commercial:

i. Summary of batch numbers

Batch number(s) of the FPPs used in			
Bioequivalence or biowaiver			
Dissolution profile studies			
Stability studies (primary batches)			
‹packaging configuration I›			
‹packaging configuration II›			
‹Add/delete as many rows as necessary›			
Stability studies (production batches)			
‹packaging configuration I›			
‹packaging configuration II›			
(Add/delete as many rows as necessary)			
Validation studies (primary batches) if available			
‹packaging configuration I›			
‹packaging configuration II›			
(Add/delete as many rows as necessary)			
Validation studies (at least the first three consecutive production batches) or code(s)/version(s) for process validation protocol(s)			

ii. Summary of formulations and discussion of any differences:

Component and quality standard (e.g. NF, BP, Ph.Eur, in-house)	**Relevant batches**							
	Comparative bioavailability or biowaiver		**Stability**		**Process validation**		**Commercial (2.3.P.1)**	
	<Batch nos. and sizes>		**<Batch nos. and sizes>**		**<Batch nos. and sizes>**		**<Batch nos. and sizes>**	
	Theor. quantity per batch	**%**	**Theor. quantity per batch**	**%**	**Theor. quantity per batch**	**%**	**Theor. quantity per batch**	**%**
<complete with appropriate title e.g. Core tablet, Contents of capsule, Powder for injection>								
Subtotal 1								
<complete with appropriate title e.g. Film-coating>								
Subtotal 2								
Total								

c) Description of batches used in the comparative in vitro studies (e.g. dissolution) and in the in vivo studies (e.g. comparative bioavailability or biowaiver), including strength, batch number, type of study and reference to the data (volume, page):

d) Summary of results for comparative in vitro studies (e.g. dissolution)

e) Summary of any information on in vitro-in vivo correlation (IVIVC) studies (with cross-reference to the studies in Module 5):

f) For scored tablets, provide the rationale/justification for scoring:

2.3.P.2.2.2 Overages

a) Justification of overages in the formulation(s) described in 2.3.P.1: (e.g. pH, ionic strength, dissolution, particle size distribution, polymorphism, rheological properties):

2.3.P.2.3 Manufacturing Process Development

a) Discussion of the development of the manufacturing process of the FPP (e.g. optimization of the process, selection of the method of sterilization):

b) Discussion of the differences in the manufacturing process(es) for the batches used in the comparative bioavailability or biowaiver studies and the process described in 2.3.P.3.3:

2.3.P.2.4 Container Closure System

a) Discussion of the suitability of the container closure system (described in 2.3.P.7) used for the storage, transportation (shipping) and use of the FPP (e.g. choice of materials, protection from moisture and light, compatibility of the materials with the FPP):

b) For a device accompanying a multi-dose container, a summary of the study results demonstrating the reproducibility of the device (e.g. consistent delivery of the intended volume):

2.3.P.2.5 Microbiological Attributes

a) Discussion of microbiological attributes of the FPP (e.g. preservative effectiveness studies):

2.3.P.2.6 Compatibility

a) Discussion of the compatibility of the FPP (e.g. with reconstitution diluent(s) or dosage devices, co-administered FPPs):

2.3.P.3 Manufacture

2.3.P.3.1 Manufacturer(s)

a) Name, address and responsibility (e.g. fabrication, packaging, labelling, testing) of each manufacturer, including contractors and each proposed production site or facility involved in manufacturing and testing

Name and address (include block(s)/unit(s))	**Responsibility**

2.3.P.3.2 Batch Formula

a) List of all components of the FPP to be used in the manufacturing process and their amounts on a per batch basis (including individual components of mixtures prepared in-house (e.g. coatings) and overages, if any):

Strength (label claim)			
Master production document reference number and/or version			
Proposed commercial batch size(s) (e.g. number of dosage units)			
Component and quality Standard (and grade, if applicable)	**Quantity per batch (e.g. kg/ batch)**	**Quantity per batch (e.g. kg/ batch)**	**Quantity per batch (e.g. kg/ batch)**
<complete with appropriate title e.g. Core tablet, Contents of capsule, Powder for injection>			
Subtotal 1			
<complete with appropriate title e.g. Film-coating>			
Subtotal 2			
Total			

2.3.P.3.3 Description of Manufacturing Process and Process Controls

a) Flow diagram of the manufacturing process:

b) Narrative description of the manufacturing process, including equipment type and working capacity, process parameters:

c) Justification of reprocessing of materials:

2.3.P.3.4 Controls of Critical Steps and Intermediates

a) Summary of controls performed at the critical steps of the manufacturing process and on isolated intermediates:

Step (e.g. granulation, compression, coating)	**Controls**

2.3.P.3.5 Process Validation and/or Evaluation

a) Summary of the process validation and/or evaluation studies conducted (including product quality review(s) where relevant) and/or a summary of the proposed process validation protocol for the critical steps or critical assays used in the manufacturing process (e.g. protocol number, parameters, results):

2.3.P.4 Control of Excipients

2.3.P.4.1 Specifications

a) Summary of the specifications for officially recognized compendial excipients which include supplementary tests not included in the officially recognized compendial monograph(s):

2.3.P.4.2 Analytical Procedures

a) Summary of the analytical procedures for supplementary tests:

2.3.P.4.3 Validation of Analytical Procedures

a) Summary of the validation information for the analytical procedures for supplementary tests (where applicable)

2.3.P.4.4 Justification of Specifications

a) Justification of the specifications (e.g. evolution of tests, analytical procedures and acceptance criteria, exclusion of certain tests, differences from officially recognized compendial standard(s)):

2.3.P.4.5 Excipients of Human or Animal Origin

a) For FPPs using excipients without risk of transmitting agents of animal spongiform encephalopathies, a letter of attestation confirming this can be found in: (page and volume)
b) CEP(s) demonstrating TSE-compliance can be found in: (page and volume)

2.3.P.4.6 Novel Excipients

a) 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 (non-clinical and/or clinical), should be provided according to the API and/or FPP format

2.3.P.5 Control of FPP

2.3.P.5.1 Specification(s)

Specification(s) for the FPP:

Standard (e.g. Ph.Int., BP, USP, House)			
Specification reference number and version			
Test	**Acceptance criteria (release)**	**Acceptance criteria (shelf-life)**	**Analytical procedure (type/source/version)**
Description			
Identification			
Impurities			
Assay			
etc.			

2.3.P.5.2 Analytical Procedures

a) Summary of the analytical procedures (e.g. key method parameters, conditions, system suitability testing):

2.3.P.5.3 Validation of Analytical Procedures

a) Summary of the validation information (e.g. validation parameters and results):

2.3.P.5.4 Batch Analyses

1. Description of the batches:
2. Summary of batch analyses release results for relevant batches (e.g. comparative bioavailability or biowaiver, stability):

Test	**Acceptance criteria**	**Results**		
		<batch x>	**<batch y>**	**etc.**
Description				
Identification				
Impurities				
Assay				
etc.				

3. Summary of analytical procedures and validation information for those procedures not previously summarized in 2.3.P.5.2 and 2.3.P.5.3 (e.g. historical analytical procedures):

2.3.P.5.5 Characterisation of Impurities

a) Identification of potential and actual impurities:

Degradation product (chemical name or descriptor)	**Structure**	**Origin**

Process-related impurity (compound name)	**Step used in the FPP manufacturing process**

b) Basis for setting the acceptance criteria for impurities:

i. Maximum daily dose (i.e. the amount of API administered per day) for the API, corresponding ICH Reporting/Identification/Qualification Thresholds for the degradation products in the FPP and the concentration limits (ppm) for the process-related impurities (e.g. residual solvents):

Maximum daily dose for the API:	**<x mg/day>**	
Test	**Parameter**	**ICH threshold or concentration limit**
Degradation product	Reporting Threshold	
	Identification Threshold	
	Qualification Threshold	
Process-related impurities	<solvent 1>	
	<solvent 2>, etc.	

ii. Data on observed impurities for relevant batches (e.g. comparative bioavailability or biowaiver):

Impurity (degradation product and process-related)	**Acceptance criteria**	**Results**		
		<batch no., strength, use>		

iii. Justification of proposed acceptance criteria for impurities:

2.3.P.5.6 Justification of Specification(s)

a) Justification of the FPP specification(s) (e.g. evolution of tests, analytical procedures and acceptance criteria, differences from officially recognized compendial standard(s))

2.3.P.6 Reference Standards or Materials

a) Source (including lot number) of primary reference standards or reference materials (e.g. Ph.Int., Ph.Eur., BP, USP, in-house) not discussed in 3.2.S.5:

b) Characterization and evaluation of non-official (e.g. not from an officially recognized pharmacopoeia) primary reference standards or reference materials (e.g. elucidation of structure, certificate of analysis) not discussed in 3.2.S.5:

c) Description of the process controls of the secondary reference standard (comparative certificate of analysis and IR spectra against primary standard) not discussed in 3.2.S.5:

2.3.P.7 Container Closure System

a) Description of the container closure systems, including unit count or fill size, container size or volume:

Description (including materials of construction)	**Strength**	**Unit count or fill size**	**Container size**

b) Summary of specifications of each primary and functional secondary (e.g. foil pouches) packaging components:

Packaging component	**Specifications (list parameters e.g. identification (IR))**
HDPE bottle	
PP cap	
Induction sealed liners	
Blister films (PVC, etc)	
Aluminum foil backing	
etc.	

c) Other information on the container closure system(s):

2.3.P.8 Stability

2.3.P.8.1 Stability Summary and Conclusions

a) Summary of stress testing and results (e.g. photostability studies, cyclic studies, freeze-thaw studies):

b) Summary of accelerated and long-term testing parameters (e.g. studies conducted):

Storage conditions (◦C, % RH)	Strength and batch number	Batch size	Container closure system	Completed (and proposed) test intervals

Summary of the stability results observed for the above accelerated and long-term studies:

Test	Results
Description	
Moisture	
Impurities	
Assay	
etc.	

c) Proposed storage statement and shelf-life (and in-use storage conditions and in-use period, if applicable):

Container closure system	Storage statement	Shelf-life

2.3.P.8.2 Post-approval Stability Protocol and Stability Commitment

a) Stability protocol for Primary stability batches (e.g. storage conditions (including tolerances), batch numbers and batch sizes, tests and acceptance criteria, testing frequency, container closure system(s)):

Parameter	Details	
Storage condition(s) (◦C, % RH)		
Batch number(s) / batch size(s)		
Tests and acceptance criteria	Description	
	Moisture	
	Impurities	
	Assay	
	etc.	
Testing frequency		
Container closure system(s)		

b) Stability protocol for Commitment batches (e.g. storage conditions (including tolerances), batch numbers (if known) and batch sizes, tests and acceptance criteria, testing frequency, container closure system(s)):

Parameter	Details	
Storage condition(s) (◦C, % RH)		
Batch number(s) / batch size(s)	*<not less than three production batches in each container closure system>*	
Tests and acceptance Criteria	Description	
	Moisture	
	Impurities	
	Assay	
	etc.	
Testing Frequency		
Container Closure System(s)		

c) Stability protocol for Ongoing batches (e.g. storage conditions (including tolerances), number of batches per strength and batch sizes, tests and acceptance criteria, testing frequency, container closure system(s)):

Parameter	Details	
Storage condition(s) (◦C, % RH)		
Batch size(s), annual allocation	*<at least one production batch per year (unless none is produced that year)in each container closure system >*	
Tests and acceptance Criteria	Description	
	Moisture	
	Impurities	

Parameter	Details	
	Assay	
	etc.	
Testing frequency		
Container closure system(s)		

2.3.P.8.3 Stability Data

a) The actual stability results should be provided in *Module 3*.

b) Summary of analytical procedures and validation information for those procedures *not* previously summarized in 2.3.P.5 (e.g. analytical procedures used only for stability studies):

c) Bracketing and matrixing design and justification for *Commitment* and/or *Ongoing stability batches*, if applicable:

2.3.A APPENDICES

2.3.A.1 Facilities and Equipment

a) Summary of information on facilities and equipment, in addition to the information provided in other sections of the submission: Not applicable.

2.3.A.2 Adventitious Agents Safety Evaluation

a) Summary of the information assessing the risk with respect to potential contamination with adventitious agents: Not applicable.

2.3.A.3 Excipients

a) **Summary of the details of manufacture, characterization and controls, with cross references to supporting safety data (nonclinical and/or clinical) for the novel excipients:** Not applicable. Novel excipients are not accepted in the Prequalification Programme. See quality guideline for definition.

2.3.R REGIONAL INFORMATION

2.3.R.1 Production Documentation

2.3.R.1.1 Executed Production Documents

a) List of batches (including strengths) for which executed production documents have been provided (e.g. comparative bioavailability or biowaiver batches):

2.3.R.1.2 Master Production Documents

b) The blank master production documents for each strength, proposed commercial batch size and manufacturing facility should be provided in Module 3

2.3.R.2 Analytical Procedures and Validation Information

Number range CHAPTERANALYTICAL PROCEDURES AND VALIDATION INFORMATION SUMMARIES			
Number range CHAPTER**ATTACHMENT NUMBER:**			
HPLC Method Summary		**Volume/Page:**	
Method name:			
Method code:		**Version and/or Date:**	
Column(s) / temperature (if other than ambient):			
Mobile phase (specify gradient program, if applicable):			
Detector (and wavelength, if applicable):			
Flow rate:			
Injection volume:			
Sample solution concentration (expressed as mg/ml, let this be termed "A"):			
Reference solution concentration (expressed as mg/ml and as % of "A"):			
System suitability solution concentration (expressed as mg/ml and as % of "A"):			
System suitability tests (tests and acceptance criteria):			
Method of quantification (e.g. against API or impurity reference standard(s)):			
Other information (specify):			

Number range CHAPTER**ATTACHMENT NUMBER:**					
Validation Summary		**Volume/Page:**			
Analytes:					
Typical retention times (RT)					
Relative retention times ($RT_{Imp.}/RT_{API\ or\ Int.\ Std.}$):					
Relative response factor ($RF_{Imp.}/RF_{API}$):					
Specificity:					
Linearity / Range:	Number of concentrations: Range (expressed as % "A"): Slope: Y-intercept: Correlation coefficient (r^2) :				

Number range CHAPTER**ATTACHMENT NUMBER:**					
Accuracy:	Conc.(s) (expressed as % "A"): Number of replicates: Percent recovery (avg/RSD):				
Precision / Repeatability: (intra-assay precision)	Conc.(s) (expressed as % "A"): Number of replicates: Result (avg/RSD):				
Precision / Intermediate Precision: (days/analysts/equipment)	Parameter(s) altered: Result (avg/RSD):				
Limit of Detection (LOD): (expressed as % "A")					
Limit of Quantitation (LOQ): (expressed as % "A")					
Robustness:	Stability of solutions: Other variables/effects:				
Typical chromatograms or spectra may be found in:					
Company(s) responsible for method validation:					
Other information (specify):					

ANNEX VIII: Product Quality Review (PQR) requirements for generic pharmaceutical products

For an established generic product, a product quality review may satisfy the requirements of sections 3.2.P.2.2.1 (a), 3.2.P.2.3 (a) and 3.2.P.3.5 of the PD and QOS-PD.

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.

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:

a) A review of starting and primary packaging materials used in the FPP, especially those from new sources.

b) A tabulated review and statistical analysis of quality control and in-process control results.

c) A review of all batches that failed to meet established specification(s).

d) A review of all critical deviations or non-conformances and related investigations.

e) A review of all changes carried out to the processes or analytical methods.

f) A review of the results of the stability-monitoring programme.

g) A review of all quality-related returns, complaints and recalls, including export- only medicinal products.

h) A review of the adequacy of previous corrective actions.

i) A list of validated analytical and manufacturing procedures and their revalidation dates.

Notes

Reviews must include data from all batches manufactured during the review period. Data should be presented in tabular or graphical form (i.e. charts or graphs), when applicable.

PART II:

GUIDELINES ON STABILITY TESTING REQUIREMENTS FOR ACTIVE PHARMACEUTICAL INGREDIENTS (APIs) AND FINISHED PHARMACEUTICAL PRODUCTS (FPPs)

ABBREVIATIONS AND ACRONYMS

APIs:	Active Pharmaceutical Ingredient
PPB:	East Africa Community
FDC:	Fixed Dose Combination
FPP:	Finished Pharmaceutical Product
FPPs:	Finished Medicinal Products
ICH:	International Conference on Harmonization
LVPs:	Large Volume Parenterals
NMT:	Not More Than
RH:	Relative Humidity
SVPs:	Small Volume Parenterals

GLOSSARY

The definitions provided below apply to the words and phrases used in this guideline. Although an effort has been made to use standard definitions as far as possible, they may have different meanings in other contexts and documents. The following definitions are provided to facilitate interpretation of the guidelines. The definitions are consistent with those published in other WHO quality assurance guidelines.

Accelerated testing

Studies designed to increase the rate of chemical degradation and physical change of an API or FPP by using exaggerated storage conditions as part of the stability testing programme. The data thus obtained, in addition to those derived from long-term stability studies, may be used to assess longer term chemical effects under non-accelerated conditions and to evaluate the impact of short-term excursions outside the label storage conditions, as might occur during shipping. The results of accelerated testing studies are not always predictive of physical changes.

Bracketing

The design of stability schedule such that only samples at the extremes of certain design factors, e.g. strength and package size, are tested at all-time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested.

Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or very closely related in composition (e.g. for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells). Bracketing can be applied to different container sizes or different fills in the same container closure system.

Commitment batches

Production batches of an API or FPP for which the stability studies are initiated or completed post-approval through a commitment made in a regulatory application.

Impermeable containers

Containers that provide a permanent barrier to the passage of gases or solvents e.g. sealed aluminium tubes for semisolids, sealed glass ampoules for solutions and aluminium/aluminium blisters for solid dosage forms.

In use

See Utilization period

Long-term stability studies

Experiments on the physical, chemical, biological, biopharmaceutical and microbiological characteristics of an API or FPP, during and beyond the expected shelf-life and storage periods of samples under the storage conditions expected in the intended market. The results are used to establish the re-test period or the shelf-life, to confirm the projected re-test period and shelf-life, and to recommend storage conditions.

Matrixing

The design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations is tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same FPP should be identified as, for example, covering different batches, different strengths, different sizes of the same container closure system, and, possibly in some cases, different container closure systems.

On-going 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 confirm or extend the shelf-life of the FPP.

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.

Provisional shelf-life

A provisional expiry date which is based on acceptable accelerated and available long-term data for the FPP to be marketed in the proposed container closure system.

Re-test date

The date after which an active API should be re-examined to ensure that the material is still in compliance with the specification and thus is still suitable for use in the manufacture of an FPP.

Re-test period

The period of time during which the API is expected to remain within its specification and, therefore, can be used in the manufacture of a given FPP, provided that the API has been stored under the defined conditions. After this period a batch of API destined for use in the manufacture of an FPP should be re-tested for compliance with the specification and then used immediately. A batch of API can be re-tested multiple times and a different portion of the batch used after each re-test, as long as it continues to comply with the specification. For most substances known to be labile, it is more appropriate to establish a shelf-life than a re-test period. The same may be true for certain antibiotics.

Significant change (See section 2.2.6.1.)

In general "significant change" for an FPP is defined as:

a) A 5% or more change in assay from its initial content of API(s), or failure to meet the acceptance criteria for potency when using biological or immunological procedures. (*Note*: other values may be applied, if justified, to certain products, such as multivitamins and herbal preparations.)

b) Any degradation product exceeding its acceptance criterion.

c) Failure to meet the acceptance criteria for appearance, physical attribute and functionality test (e.g. colour, phase separation, re-suspendability, caking, hardness, dose delivery per actuation). However, some changes in physical attributes (e.g. softening of suppositories, melting of creams or partial loss of adhesion for transdermal products) may be expected under accelerated conditions. Also, as appropriate for the dosage form.

d) Failure to meet the acceptance criterion for pH.

e) Failure to meet the acceptance criteria for dissolution for 12 dosage units.

Stability indicating methods

Validated analytical procedures that can detect the changes with time in the chemical, physical or microbiological properties of the API or FPP, and that are specific so that the content of the API, degradation products, and other components of interest can be accurately measured without interference.

Stability studies (stability testing)

Long-term and accelerated (and intermediate) studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the re-test period (or shelf-life) of an API or the shelf-life of an FPP.

Stress testing (of the API)

Studies undertaken to elucidate the intrinsic stability of API(s). Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing.

Stress testing (of the FPP)

Studies undertaken to assess the effect of severe conditions on the FPP. Such studies include photo stability testing and specific testing on certain products (e.g. metered dose inhalers, creams, emulsions, refrigerated aqueous liquid products).

Supporting stability data

Supplementary data, such as stability data on small-scale batches, related formulations, and products presented in containers not necessarily the same as those proposed for marketing, and scientific rationales that support the analytical procedures, the proposed re-test period or the shelf-life and storage conditions.

Utilization period

A period of time during which a reconstituted preparation of the finished dosage form in an unopened multi-dose container can be used.

1. INTRODUCTION

1.1 Objective

The guideline describes the core stability data package required for active pharmaceutical ingredients (APIs) and finished medicinal products (FPPs). However, alternative approaches can be used when they are scientifically justified. The guideline is adopted from WHO Technical Report Series, No. 953, Annex II. Further guidance can be found in International Conference on Harmonisation (ICH) guidelines (3) and in the WHO guidelines on the active pharmaceutical ingredient master file procedure (4).

It is recommended that the guideline should also be applied to products that are already being marketed, with allowance for an appropriate transition period, e.g. upon re-registration or upon re-evaluation.

1.2 Scope

The guideline applies to new and existing APIs and addresses information to be submitted in original and subsequent applications for marketing authorization of their related FPP for human use. The guideline is not applicable to stability testing for biologicals (for details on vaccines please see WHO guidelines for stability evaluation of vaccines (5)).

1.3 General principles

The purpose of stability testing is to provide evidence of how the quality of an API or FPP varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The stability programme also includes the study of product-related factors that influence its quality, for example, interaction of API with excipients, container closure systems and packaging materials. In fixed-dose combination FPPs (FDCs) the interaction between two or more APIs also has to be considered.

As a result of stability testing a re-test period for the API (in exceptional cases, e.g. for unstable APIs, a shelf-life is given) or a shelf-life for the FPP can be established and storage conditions can be recommended.

2. REQUIREMENT

2.1 Active pharmaceutical ingredients

2.1.1 General

Information on the stability of the API is an integral part of the systematic approach to stability evaluation. Potential attributes to be tested on an API during stability testing are listed in the examples of testing parameters.

The re-test period or shelf-life assigned to the API by the API manufacturer should be derived from stability testing data.

2.1.2 Stress testing

Stress testing of the API can help identify the likely degradation products, which, in turn, can 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.

For an API the following approaches may be used:

- when available, it is acceptable to provide the relevant data published in the scientific literature to support the identified degradation products and pathways;
- when no data are available, stress testing should be performed.

Stress testing may be carried out on a single batch of the API. It should include the effect of temperature (in 10 °C increments (e.g. 50 °C, 60 °C, e.t.c.) above the temperature used for accelerated testing), humidity (e.g. 75% relative humidity (RH) or greater) and, where appropriate, acid stress, alkaline stress, oxidation and photolysis on the API. The testing should also evaluate the susceptibility of the API to hydrolysis across a justified range of pH values when in solution or suspension (*10*).

Assessing the necessity for photostability testing should be an integral part of a stress testing strategy. More details can be found in other guidelines (3).

Results from these studies will form an integral part of the information provided to regulatory authorities.

2.1.3 Selection of batches

Data from stability studies on at least three primary batches of the API should normally be provided. The batches should be manufactured to a minimum of pilot scale 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 overall quality of the batches of API placed on stability studies should be representative of the quality of the material to be made on a production scale.

For existing active substances that are known to be stable, data from at least two primary batches should be provided.

2.1.4 Container closure system

The stability studies should be conducted on the API packaged in a container closure system that is the same as, or simulates, the packaging proposed for storage and distribution.

2.1.5 Specification

Stability studies should include testing of those attributes of the API that are susceptible to change during storage and are likely to influence quality, safety and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological and microbiological attributes. A guide as to the potential attributes to be tested in the stability studies is provided in Appendix 1.

Validated stability-indicating analytical procedures should be applied. Whether and to what extent replication should be performed will depend on the results from validation studies (11).

2.1.6 Testing frequency

For long-term studies, frequency of testing should be sufficient to establish the stability profile of the API.

For APIs with a proposed re-test period or shelf-life of at least 12 months, the frequency of testing at the long-term storage condition should normally be every three months over the first year, every six months over the second year, and annually thereafter throughout the proposed re-test period or shelf-life.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g. 0, 3 and 6 months), from a six month study is recommended. Where it is expected (based on development experience) that results from accelerated studies are likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design.

2.1.7 Storage conditions

In general, an API should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture. The storage conditions and the lengths of studies chosen should be sufficient to cover storage and shipment.

Storage condition tolerances are defined as the acceptable variations in temperature and relative humidity of storage facilities for stability studies. The equipment used should be capable of controlling the storage conditions within the ranges defined in these guidelines. The storage conditions should be monitored and recorded. Short-term environmental changes due to opening the doors of the storage facility are accepted as unavoidable. The effect of excursions due to equipment failure should be assessed, addressed and reported if judged to affect stability results. Excursions that exceed the defined tolerances for more than 24 hours should be described in the study report and their effects assessed.

The long-term testing should normally take place over a minimum of 12 months for the number of batches specified in section 2.1.3 at the time of submission, and should be continued for a period of time sufficient to cover the proposed re-test period or shelf-life. For existing substances that are known to be stable, data covering a minimum of six months may be submitted. Additional data accumulated during the assessment period of the registration application should be submitted to the authorities upon request.

Available information on the stability of the API under accelerated and long - term storage conditions should be provided, including information in the

public domain or obtained from scientific literature. The source of the information should be identified.

The required long-term storage conditions for APIs by PPB countries are either 300C±2 0C/65%±5% RH or 30±20C/75%±5% RH. Alternative conditions should be supported with appropriate evidence, which may include literature references or in-house studies, demonstrating that storage at 300C is inappropriate for the API. For APIs intended for storage in a refrigerator and those intended for storage in a freezer, refer section 2.1.7.1.

APIs intended for storage below -20 °C should be treated on a case-by-case basis. To establish the retest 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 a procedure that simulates the final process to be used for production batches.

2.1.7.1 General case

Study Storage Condition Minimum time period covered by data at submission

Long-term

30 °C ± 2 °C/65% RH ± 5% RH or

30 °C ± 2 °C/75% RH ± 5% RH

12 months or 6 months as described in point 2.1.7

Accelerated

40 °C ± 2 °C/75% RH ± 5% RH 6 months

2.1.7.2 Active pharmaceutical ingredients intended for storage in a refrigerator

Study Storage Condition Minimum time period covered by data at submission

Long-term

5 °C ± 3 °C 12 months

Accelerated

25 °C ± 2 °C/60% RH ± 5% RH or

30 °C ± 2 °C/65% RH ± 5% RH or

30 °C ± 2 °C/75% RH ± 5% RH

6 months

Whether accelerated stability studies are performed at 25 ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ±5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is based on a risk-based evaluation. Testing at a more severe long-term condition can be an alternative to storage testing at 25 °C/60%RH or 30 °C/65%RH. Data on refrigerated storage should be assessed according to the evaluation section of this guideline, except where explicitly noted below. If significant change occurs between three, and six months' testing at the accelerated storage condition, the proposed re-test period should be based on the data available at the long-term storage condition. If significant change occurs within the first three months' testing at the accelerated storage condition a discussion should be provided to address the effect of short-term excursions outside the label storage condition, e.g. during shipping or handling. This discussion can be supported, if appropriate, by further testing on a single batch of the API for a period shorter than three months but with more frequent testing than usual. It is considered unnecessary to continue to test an API for the whole six months when a significant change has occurred within the first three months.

2.1.7.3 Active pharmaceutical ingredients intended for storage in a freezer

Study Storage Condition Minimum time period covered by data at submission

Long-term

20 °C ± 5 °C 12 months

In the rare case of any API of non-biological origin being intended for storage in a freezer, the re-test period or shelf-life should be based on the long-term

data obtained at the long-term storage condition. In the absence of an accelerated storage condition for APIs intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g. 5 °C ± 3 °C or 25°C ± 2 °C or 30 °C ± 2 °C) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition, e.g. during shipping or handling.

2.1.7.4 Active pharmaceutical ingredients intended for storage below 20°C

APIs intended for storage below 20 °C should be treated on a case-by-case basis.

2.1.8 Stability commitment

When the available long-term stability data on primary batches do not cover the proposed re-test, period granted at the time of approval, a commitment should be made to continue the stability studies post-approval in order to firmly establish the re-test period or shelf-life.

Where the submission includes long-term stability data on the number of production batches specified in section 2.1.3 covering the proposed re-test period, a post-approval commitment is considered unnecessary. Otherwise one of the following commitments should be made:

- If the submission includes data from stability studies on the number of production batches specified in section 2.1.3, a commitment should be made to continue these studies through the proposed re-test period.
- If the submission includes data from stability studies on fewer than the number of production batches specified in section 2.1.3, a commitment should be made to continue these studies through the proposed re-test period and to place additional production batches, to a total of at least three, in long-term stability studies through the proposed re-test period.
- If the submission does not include stability data on production batches, a commitment should be made to place the first two or three production

batches (see section 2.1.3) on long-term stability studies through the proposed re-test period.

The stability protocol used for long-term studies for the stability commitment should be the same as that for the primary batches, unless otherwise scientifically justified.

2.1.9 Evaluation

The purpose of the stability study is to establish, based on testing a minimum of the number of batches specified in section 2.1.3, unless otherwise justified and authorized, of the API and evaluating the stability information (including, as appropriate, results of the physical, chemical, biological and microbiological tests), a re-test period applicable to all future batches of the API manufactured under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout the assigned re-test period.

The data may show so little degradation and so little variability that it is apparent from looking at them that the requested re-test period will be granted. Under these circumstances, it is normally unnecessary to go through the statistical analysis; providing a justification for the omission should be sufficient.

An approach for analysing the data on a quantitative attribute that is expected to change with time is to determine the time at which the 95% one-sided confidence limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g. p values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall re-test period should be based on the minimum time a batch can be expected to remain within acceptance criteria.

The nature of any degradation relationship will determine whether the data should be transformed for linear regression analysis. Usually, the relationship

can be represented by a linear, quadratic or cubic function on an arithmetic or logarithmic scale. As far as possible, the choice of model should be justified by a physical and/or chemical rationale and should also take into account the amount of available data (parsimony principle to ensure a robust prediction). Statistical methods should be employed to test the goodness of fit of the data on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

Limited extrapolation of the long-term data from the long-term storage condition beyond the observed range to extend the re-test period can be undertaken if justified. This justification should be based on what is known about the mechanism of degradation, the results of testing under accelerated conditions, the goodness of fit of any mathematical model, batch size and existence of supporting stability data. However, this extrapolation assumes that the same degradation relationship will continue to apply beyond the observed data.

Any evaluation should cover not only the assay but also the levels of degradation products and other appropriate attributes. Where appropriate, attention should be paid to reviewing the adequacy of evaluation linked to FPP stability and degradation "behaviour" during the testing.

2.1.10 Statements and labelling

A storage statement should be established for display on the label based on the stability evaluation of the API. Where applicable specific instructions should be provided, particularly for APIs that cannot tolerate freezing or excursions in temperature. Terms such as "ambient conditions" or "room temperature" should be avoided.

The recommended labelling statements for use if supported by the stability studies are provided in Appendix 2.

A re-test period should be derived from the stability information, and a retest date should be displayed on the container label if appropriate.

2.1.11 On-going stability studies

The stability of the API should be monitored according to a continuous and appropriate programme that will permit the detection of any stability issue (e.g. changes in levels of degradation products). The purpose of the on-going stability programme is to monitor the API and to determine that the API remains, and can be expected to remain, within specifications under the storage conditions indicated on the label, within the re-test period in all future batches.

The on-going stability programme should be described in a written protocol and the results presented in a formal report.

The protocol for an on-going stability programme should extend to the end of the re-test period and shelf-life and should include, but not be limited to, the following parameters:

i. number of batch (es) and different batch sizes, if applicable;
ii. relevant physical, chemical, microbiological and biological test methods;
iii. acceptance criteria;
iv. reference to test methods;
v. description of the container closure system(s);
vi. testing frequency;
vii. description of the conditions of storage (standardized conditions for long-term testing as described in these guidelines, and consistent with the API labelling, should be used); and
viii. other applicable parameters specific to the API.

At least one production batch per year of API (unless none is produced during that year) should be added to the stability monitoring programme and tested at least annually to confirm the stability (12). In certain situations, additional batches should be included in the on-going stability programme. For example, an on-going stability study should be conducted after any significant change

or significant deviation to the synthetic route, process or container closure system which may have an impact upon the stability of the API (13).

Out-of-specification results or significant atypical trends should be investigated. Any confirmed significant change, out-of-specification result, or significant atypical trend should be reported immediately to the relevant finished product manufacturer. The possible impact on batches on the market should be considered in consultation with the relevant finished product manufacturers and the competent authorities.

A summary of all the data generated, including any interim conclusions on the programme, should be written and maintained. This summary should be subjected to periodic review.

2.2 Finished medicinal product

2.2.1. General

The design of the stability studies for the FPP should be based on knowledge of the behaviour and properties of the API, information from stability studies on the API and on experience gained from pre-formulation studies and investigational FPPs.

2.2.2. Selection of batches

Data from stability studies should be provided on at least three primary batches of the FPP. The primary batches should be of the same formulation and packaged in the same container closure system as proposed for marketing. The manufacturing process used for primary batches should simulate that to be applied to production batches and should provide product of the same quality and meeting the same specification as that intended for marketing. In the case of conventional dosage forms with APIs that are known to be stable, data from at least two primary batches should be provided.

Two of the three batches should be at least pilot-scale batches and the third one can be smaller, if justified. Where possible, batches of the FPP should be manufactured using different batches of the API(s).

Stability studies should be performed on each individual strength, dosage form and container type and size of the FPP unless bracketing or matrixing is applied.

2.2.3. Container closure system

Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing. Any available studies carried out on the FPP outside its immediate container or in other packaging materials can form a useful part of the stress testing of the dosage form or can be considered as supporting information, respectively.

2.2.4. Specification

Stability studies should include testing of those attributes of the FPP that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological and microbiological attributes, preservative content (e.g. antioxidant or antimicrobial preservative) and functionality tests (e.g. for a dose delivery system). Examples of testing parameters in the stability studies are listed in Appendix 1. Analytical procedures should be fully validated and stability-indicating. Whether and to what extent replication should be performed will depend on the results of validation studies.

Shelf-life acceptance criteria should be derived from consideration of all available stability information. It may be appropriate to have justifiable differences between the shelf-life and release acceptance criteria based on the stability evaluation and the changes observed on storage. Any differences between the release and shelf-life acceptance criteria for antimicrobial preservative content should be supported by a validated correlation of chemical content and preservative effectiveness demonstrated during development of the pharmaceutical product with the product in its final formulation (except for preservative concentration) intended for marketing. A single primary stability batch of the FPP should be tested for effectiveness of the antimicrobial preservative (in addition to preservative content) at the proposed shelf-life for verification purposes, regardless of whether there is a

difference between the release and shelf-life acceptance criteria for preservative content.

2.2.5. Testing frequency

For long-term studies, frequency of testing should be sufficient to establish the stability profile of the FPP.

For products with a proposed shelf-life of at least 12 months, the frequency of testing at the long-term storage condition should normally be every three months over the first year, every six months over the second year and annually thereafter throughout the proposed shelf-life.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g. 0, 3 and 6 months), from a six-month study is recommended. Where an expectation (based on development experience) exists that results from accelerated testing are likely to approach significant change criteria, testing should be increased either by adding samples at the final time point or by including a fourth time point in the study design.

Reduced designs, i.e. matrixing or bracketing, where the testing frequency is reduced or certain factor combinations are not tested at all, can be applied if justified (3).

2.2.6. Storage conditions

In general, an FPP should be evaluated under storage conditions with specified tolerances that test its thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment and subsequent use with due regard to the climatic conditions in which the product is intended to be marketed.

Photostability testing, which is an integral part of stress testing, should be conducted on at least one primary batch of the FPP if appropriate. More details can be found in other guidelines (3).

The orientation of the product during storage, i.e. upright versus inverted, may need to be included in a protocol where contact of the product with the closure system may be expected to affect the stability of the products contained, or where there has been a change in the container closure system.

Storage condition tolerances are usually defined as the acceptable variations in temperature and relative humidity of storage facilities for stability studies. The equipment used should be capable of controlling the storage conditions within the ranges defined in these guidelines. The storage conditions should be monitored and recorded. Short-term environmental changes due to opening of the doors of the storage facility are accepted as unavoidable. The effect of excursions due to equipment failure should be assessed, addressed and reported if judged to affect stability results.

Excursions that exceed the defined tolerances for more than 24 hours should be described in the study report and their effects assessed. The long-term testing should cover a minimum of six or 12 months at the time of submission and should be continued for a period of time sufficient to cover the proposed shelf-life. For an FPP containing an API that is known to be stable and where no significant change is observed in the FPP stability studies at accelerated and long-term conditions for at least 6 months' data covering a minimum of six months should be submitted.

Additional data accumulated during the assessment period of the registration application should be submitted to the authorities if requested. Data from the accelerated storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping). Long-term and accelerated storage conditions for FPPs are detailed in the sections below. The general case applies if the FPP is not specifically covered by a subsequent section (2.1.7.1). Alternative storage conditions can be used if justified.

2.2.6.1 General case

Study Storage Condition Minimum time period covered by data at submission

Long-term

30 °C ± 2 °C/75% RH ± 5% RH

12 months or Claimed shelf life as referred to in section 2.2.6

Accelerated

40 °C ± 2 °C/75% RH ± 5% RH 6 months

In general, "significant change" for an FPP is defined as:

i. A change from the initial content of API(s) of 5% or more detected by assay, or failure to meet the acceptance criteria for potency when using biological or immunological procedures. (*Note*: Other values may be applied, if justified, to certain products, such as multivitamins and herbal preparations.)

ii. Any degradation product exceeding its acceptance criterion.

iii. Failure to meet the acceptance criteria for appearance, physical attribute and functionality test (e.g. colour, phase separation, resuspendability, caking, hardness, and dose delivery per actuation). However, some changes in physical attributes (e.g. softening of suppositories, melting of creams, and partial loss of adhesion for transdermal products) may be expected under accelerated conditions. Also, as appropriate for the dosage form:

iv. failure to meet the acceptance criterion for pH; or

v. failure to meet the acceptance criteria for dissolution for 12 dosage units.

2.2.6.2 FPPs packaged in impermeable containers

Parameters required to classify the packaging materials as permeable or impermeable depend on the characteristics of the packaging material, such as thickness and permeability coefficient. The suitability of the packaging material used for a particular product is determined by its product characteristics. Containers generally considered to be moisture impermeable include glass ampoules.

Sensitivity to moisture or potential for solvent loss is not a concern for FPPs packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus, stability studies for products stored in impermeable containers can be conducted under any controlled or ambient relative humidity condition.

2.2.6.3 FPPs packaged in semi-permeable containers

Aqueous-based products packaged in semi-permeable containers should be evaluated for potential water loss in addition to physical, chemical, biological and microbiological stability. This evaluation can be carried out under conditions of low relative humidity, as discussed below. Ultimately it should be demonstrated that aqueous-based FPPs stored in semi-permeable containers could withstand environments with low relative humidity.

Other comparable approaches can be developed and reported for non-aqueous, solvent-based products.

Study Storage Condition Minimum time period covered by data at submission

Long-term

30 °C ± 2 °C/35% RH ± 5% RH

12 months

Accelerated

40 °C ± 2 °C/not more than

(NMT) 25% RH

6 months

Products meeting the long-term storage conditions and the accelerated conditions, as specified in the table above, have demonstrated the integrity of the packaging in semi-permeable containers.

A 5% loss in water from its initial value is considered a significant change for a product packaged in a semi-permeable container after an equivalent of three months' storage at 40 °C not more than (NMT) 25% RH. However, for small

containers (1 ml or less) or unit-dose products, a water loss of 5% or more after an equivalent of three months' storage at 40 °C/NMT 25% RH may be appropriate, if justified.

An alternative approach to studies at the low relative humidity as recommended in the table above (for either long-term or accelerated testing) is to perform the stability studies under higher relative humidity and deriving the water loss at the low relative humidity through calculation. This can be achieved by experimentally determining the permeation coefficient for the container closure system or, as shown in the example below, using the calculated ratio of water loss rates between the two humidity conditions at the same temperature. The permeation coefficient for a container closure system can be experimentally determined by using the worst-case scenario (e.g. the most diluted of a series of concentrations) for the proposed FPP.

2.2.6.4 FPPs intended for storage in a refrigerator

Study Storage Condition Minimum time period covered by data at submission

Long-term

5 °C ± 3 °C 12 months

Accelerated

25 °C ± 2 °C/60% RH ± 5% RH or

30 °C ± 2 °C/65% RH ± 5% RH or

30 °C ± 2 °C/75% RH ± 5% RH

6 months

Whether accelerated stability studies are performed at 25 ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is based on a risk-based evaluation. Testing at a more severe accelerated condition can be an alternative to the storage condition at 25 °C/60% RH or 30 °C/65% RH.

If the FPP is packaged in a semi-permeable container, appropriate information should be provided to assess the extent of water loss.

Data from refrigerated storage should be assessed according to the evaluation section of these guidelines, except where explicitly noted below.

If significant change occurs between three- and six-months' testing at the accelerated storage condition, the proposed shelf-life should be based on the data available from the long-term storage condition.

If significant change occurs within the first three months' testing at the accelerated storage condition, a discussion should be provided to address the effect of short-term excursions outside the label storage condition, e.g. during shipment and handling. This discussion can be supported, if appropriate, by further testing on a single batch of the FPP for a period shorter than three months but with more frequent testing than usual. It is considered unnecessary to continue to test a product throughout six months when a significant change has occurred within the first three months of accelerated studies at the specific condition chosen in accordance with the risk analysis.

2.2.6.5 FPPs intended for storage in a freezer

Study Storage condition Minimum time period covered by data at submission

Long-term

–20 °C ± 5 °C 12 months

For FPPs intended for storage in a freezer, the shelf-life should be based on the long-term data obtained at the long-term storage condition. In the absence of an accelerated storage condition for FPPs intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g. 5 °C ± 3 °C or 25 °C ± 2 °C or 30 °C ± 2 °C) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition.

2.2.6.6 FPPs intended for storage below -20 °C

FPPs intended for storage at temperatures below -20 °C should be treated on a case-by-case basis.

2.2.7 Stability commitment

When the available long-term stability data on primary batches do not cover the proposed shelf-life granted at the time of approval, a commitment should be made to continue the stability studies post-approval to firmly establish the shelf-life.

Where the submission includes long-term stability data from the production batches as specified in section 2.2.2 covering the proposed shelf-life, a post-approval commitment is considered unnecessary. Otherwise, one of the following commitments should be made:

a. If the submission includes data from stability studies on at least the number of production batches specified in section 2.2.2, a commitment should be made to continue the long-term studies throughout the proposed shelf-life and the accelerated studies for six months.

b. If the submission includes data from stability studies on fewer than the number of production batches specified in section 2.2.2, a commitment should be made to continue the long-term studies throughout the proposed shelf-life and the accelerated studies for six months, and to place additional production batches, to a total of at least three, on long-term stability studies throughout the proposed shelf-life and on accelerated studies for six months.

c. If the submission does not include stability data on production batches, a commitment should be made to place the first two or three production batches (see section 2.2.2) on long-term stability studies throughout the proposed shelf-life and on accelerated studies for six months.

The stability protocol used for studies on commitment batches should be the same as that for the primary batches, unless otherwise scientifically justified.

2.2.8 Evaluation

A systematic approach should be adopted to the presentation and evaluation of the stability information, which should include, as appropriate, results from the physical, chemical, biological and microbiological tests, including particular attributes of the dosage form (for example, dissolution rate for solid oral dosage forms).

The purpose of the stability study is to establish, based on testing a minimum number of batches of the FPP as specified in section 2.2.2, a shelf-life and label storage instructions applicable to all future batches of the FPP manufactured under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout its shelf-life.

Where the data show so little degradation and so little variability that it is apparent from looking at the data that the requested shelf-life will be granted, it is normally unnecessary to go through the statistical analysis. However, a provisional shelf-life of 24 months may be established provided the following conditions are satisfied:

a) The API is known to be stable (not easily degradable).

b) Stability studies, as outlined above in section 2.1.11, have been performed and no significant changes have been observed.

c) Supporting data indicate that similar formulations have been assigned a shelf-life of 24 months or more.

d) The manufacturer will continue to conduct long-term studies until the proposed shelf-life has been covered, and the results obtained will be submitted to the national medicines regulatory authority.

e) An approach for analysing the data on a quantitative attribute that is expected to change with time is to determine the time at which the 95% one-sided confidence limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g. *p* values for level of

significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall shelf-life should be based on the minimum time a batch can be expected to remain within acceptance criteria.

The nature of any degradation relationship will determine whether the data should be transformed for linear regression analysis. Usually, the relationship can be represented by a linear, quadratic or cubic function on an arithmetic or logarithmic scale. As far as possible, the choice of model should be justified by a physical and/or chemical rationale and should also take into account the amount of available data (parsimony principle to ensure a robust prediction).

Statistical methods should be employed to test the goodness of fit of the data on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

Limited extrapolation of the long-term data from the long-term storage condition beyond the observed range to extend the shelf-life can be undertaken, if justified. This justification should be based on what is known about the mechanism of degradation, the results of testing under accelerated conditions, the goodness of fit of any mathematical model, batch size and the existence of supporting stability data. However, this extrapolation assumes that the same degradation relationship will continue to apply beyond the observed data.

Any evaluation should consider not only the assay but also the degradation products and other appropriate attributes. Where appropriate, attention should be paid to reviewing the adequacy of evaluation linked to FPP stability and degradation "behaviour" during the testing.

2.2.9 Statements and labelling

A storage statement should be established for the label based on the stability evaluation of the FPP. Where applicable, specific instructions should be

provided particularly for FPPs that cannot tolerate freezing. Terms such as “ambient conditions” or “room temperature” must be avoided.

There should be a direct link between the storage statement on the label and the demonstrated stability of the FPP. An expiry date should be displayed on the container label. The recommended labelling statements for use, if supported by the stability studies, are provided in Appendix 2.

In principle, FPPs should be packed in containers that ensure stability and protect the FPP from deterioration. A storage statement should not be used to compensate for inadequate or inferior packaging. Additional labelling statements could be used in cases where the results of the stability testing demonstrate limiting factors (see also Appendix 2).

2.2.10 In-use stability

The purpose of in-use stability testing is to provide information for the labelling on the preparation, storage conditions and utilization period of multi-dose products after opening, reconstitution or dilution of a solution, e.g. an antibiotic injection supplied as a powder for reconstitution.

As far as possible the test should be designed to simulate the use of the FPP in practice, taking into consideration the filling volume of the container and any dilution or reconstitution before use. At intervals comparable to those which occur in practice appropriate quantities should be removed by the withdrawal methods normally used and described in the product literature.

The physical, chemical and microbial properties of the FPP susceptible to change during storage should be determined over the period of the proposed in-use shelf-life. If possible, testing should be performed at intermediate time points and at the end of the proposed in-use shelf-life on the final amount of the FPP remaining in the container. Specific parameters, e.g. for liquids and semi-solids, preservatives, per content and effectiveness, need to be studied.

A minimum of two batches, at least pilot-scale batches, should be subjected to the test. At least one of these batches should be chosen towards the end of

its shelf-life. If such results are not available, one batch should be tested at the final point of the submitted stability studies.

This testing should be performed on the reconstituted or diluted FPP throughout the proposed in-use period on primary batches as part of the stability studies at the initial and final time points and, if full shelf-life, long term data are not available before submission, at 12 months or the last time point at which data will be available.

In general, this testing need not be repeated on commitment batches (see 2.2.10).

2.2.11 Variations

Once the FPP has been registered, additional stability studies are required whenever variations that may affect the stability of the API or FPP are made, such as major variations (13).

The following are examples of such changes:

— change in the manufacturing process;

— change in the composition of the FPP;

— change of the immediate packaging;

— change in the manufacturing process of an API.

In all cases of variations, the applicant should investigate whether the intended change will or will not have an impact on the quality characteristics of APIs and/or FPPs and consequently on their stability.

The scope and design of the stability studies for variations and changes are based on the knowledge and experience acquired on APIs and FPPs.

The results of these stability studies should be communicated to the regulatory authorities concerned (14).

2.2.12 On-going stability studies

After a marketing authorization has been granted, the stability of the FPP should be monitored according to a continuous appropriate programme that will permit the detection of any stability issue (e.g. changes in levels of

impurities or dissolution profile) associated with the formulation in the container closure system in which it is marketed. The purpose of the On-going stability programme is 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.

This mainly applies to the FPP in the container closure system in which it is supplied, but consideration should also be given to inclusion in the programme of bulk products. For example, when the bulk product is stored for a long period before being packaged and/or shipped from a manufacturing site to a packaging site, the impact on the stability of the packaged product should be evaluated and studied. Generally, this would form part of development studies, but where this need has not been foreseen, inclusion of a one-off study in the on-going stability programme could provide the necessary data. Similar considerations could apply to intermediates that are stored and used over prolonged periods.

The on-going stability programme should be described in a written protocol and results formalized as a report.

The protocol for an on-going stability programme should extend to the end of the shelf-life period and should include, but not be limited to, the following parameters:

a) Number of batch(es) per strength and different batch sizes, if applicable.

b) The batch size should be recorded, if different batch sizes are employed;

c) Relevant physical, chemical, microbiological and biological test

d) Methods;

e) Acceptance criteria;

f) Reference to test methods;

g) Description of the container closure system(s);

h) Testing frequency;

i) Description of the conditions of storage (standardized conditions for long-term testing as described in these guidelines, and consistent with the product labelling, should be used); and

j) Other applicable parameters specific to the FPP.

The protocol for the on-going stability programme can be different from that of the initial long-term stability study as submitted in the marketing authorization dossier provided that this is justified and documented in the protocol (for example, the frequency of testing, or when updating to meet revised recommendations).

The number of batches and frequency of testing should provide sufficient data to allow for trend analysis. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, should be included in the stability programme (unless none is produced during that year). The principle of bracketing and matrixing designs may be applied if scientifically justified in the protocol (15).

In certain situations, additional batches should be included in the on-going stability programme. For example, an on-going stability study should be conducted after any significant change or significant deviation to the processor container closure system. Any reworking, reprocessing or recovery operation should also be considered for inclusion (13).

Out-of-specification results or significant atypical trends should be investigated. Any confirmed significant change, out-of-specification result, or significant atypical trend should be reported immediately to the relevant competent authorities. The possible impact on batches on the market should be considered in consultation with the relevant competent authorities.

A summary of all the data generated, including any interim conclusions on the programme, should be written and maintained. This summary should be subjected to periodic review.

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   - International Conference on Harmonisation. *ICH Q1B: Photostability testingof new drug substances and products* (http://www.ich.org/LOB/media/MEDIA412.pdf).
   - International Conference on Harmonisation. *ICH Q1C: Stability testing of newdosage forms* (http://www.ich.org/LOB/media/MEDIA413.pdf).
   - International Conference on Harmonisation. *ICH Q1D: Bracketing andmatrixing designs for stability testing of new drug substances and products* (http://www.ich.org/LOB/media/MEDIA414.pdf).
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PART III:
GUIDELINES ON THERAPEUTIC EQUIVALENCE REQUIREMENTS AND BIO-WAVERS

ABBREVIATIONS AND ACRONYMS

$Ae_{(0-t)}$	Cumulative urinary excretion of unchanged drug from administration until time t;
APIs	Active Pharmaceutical Ingredients
$AUC_{(0-t)}$:	Area under the plasma concentration curve from administration to last observed concentration at time t;
$AUC_{(0-\infty)}$:	Area under the plasma concentration curve extrapolated to infinite time;
$AUC_{(0-t)}$:	AUC during a dosage interval at steady state;
$AUC_{(0-72h)}$	Area under the plasma concentration curve from administration to 72h;
BCS	Biopharmaceutics Classification System
BMGF	Bill and Melinda Gates Foundation
BMR	Batch Manufacturing Record
C_{max}:	Maximum plasma concentration;
$C_{max,ss}$:	Maximum plasma concentration at steady state;
CoA	Certificate of Analysis
EMA	European Medicines Agency
f_2	Similarity factor
FEAPM	Federation of East African Pharmaceutical Manufacturers
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
LTR	Local Technical Representative
MA	Marketing Authorization
MAH	Marketing Authorization Holder
PPB	Pharmacy and Poisons Board
pKa	Dissociation constant
residual area	Extrapolated area ($AUC_{(0-\infty)}$ - $AUC_{(0-t)}$)/ $AUC_{(0-\infty)}$;

R_{max}	Maximal rate of urinary excretion;
SD	Standard deviation
SmPC	Summary of Product Characteristics
t_{max}:	Time until C_{max} is reached;
$t_{max,ss}$:	Time until $C_{max,ss}$ is reached;
$t_{1/2}$:	Plasma concentration half-life;
TWG	Technical Working Group
λ_z:	Terminal rate constant;

DEFINITIONS

Absorption - the uptake of substance from a solution into or across tissues. As a time dependent process; absorption can include passive diffusion, facilitated passive diffusion (with a carrier molecule), and active transport. A Pharmaceutical product is considered to be highly absorbed when the measured extent of absorption of the highest therapeutic dose is greater or equal to (≥) 85%. High absorption: ≥ 85% of the administered dose absorbed.

Active moiety (Active): is the term used for the therapeutically active entity in the final formulation of a medicine, irrespective of the form of the API. The active is alternative terminology with the same meaning. For example, if the API is propranolol hydrochloride, the active moiety (and the active) is propranolol.

Active Pharmaceutical Ingredient (API): A substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a therapeutically active ingredient.

Bioavailability: refers to the rate and extent to which the API, or its active moiety, is absorbed from a pharmaceutical product and becomes available at the site of action. It may be useful to distinguish between the "absolute bioavailability" of a given dosage form as compared with that (100 %) following intravenous administration (e.g. oral solution *vs.* intravenous), and the "relative bioavailability" as compared with another form administered by the same or another non-intravenous route (e.g. tablets vs. oral solution).

Bioequivalence: Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and if their bioavailability in terms of peak (C_{max} and T_{max}) and total exposure (AUC) after administration of the same molar dose under the same conditions are similar to such a degree that their effects with respect to both efficacy and safety can be expected to be essentially the same. Bioequivalence focuses on the equivalence of release of the active pharmaceutical ingredient from the pharmaceutical product and its subsequent absorption into the systemic

circulation. Comparative studies using clinical or pharmacodynamic end points may also be used to demonstrate bioequivalence.

Biopharmaceutics Classification System (BCS)-based biowaivers are meant to reduce the need for establishing *in vivo* bioequivalence in situations where *in vitro* data may be considered to provide a reasonable estimate of the relative *in vivo* performance of two products. The BCS is a scientific approach designed to predict medicinal absorption based on the aqueous solubility and intestinal absorptive characteristics of the pharmaceutical product.

Biowaiver: The term biowaiver is applied to a regulatory drug approval process when the dossier (application) is approved based on evidence of equivalence other than through in vivo equivalence testing.

Comparator product: is 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.

Critical dose medicinal - Medicinal product where comparatively small differences in dose or concentration lead to dose- and concentration-dependent, serious therapeutic failures and/or serious adverse medicinal reactions which may be persistent, irreversible, slowly reversible, or life threatening, which could result in hospitalisation or prolongation of existing hospitalisation, persistent or significant disability or incapacity, or death. Adverse reactions that require significant medical intervention to prevent one of these outcomes are also considered to be serious.

Dose solubility volume (DSV) - the highest therapeutic dose [milligram (mg)] divided by the solubility of the substance [milligram/millilitre (mg/mL)] at a given pH and temperature. For example, if a pharmaceutical product has a solubility of 31 mg/mL at pH 4.5 (37°C) and the highest dose is 500 mg, then DSV = 500 mg/31 mg/mL = 16 mL at pH 4.5 (37°C).

Fixed-dose combination (FDC): A combination of two or more active pharmaceutical ingredients in a fixed ratio of doses. This term is used generically to mean a particular combination of active pharmaceutical

ingredients irrespective of the formulation or brand. It may be administered as single entity products given concurrently or as a finished pharmaceutical product.

Generic Pharmaceutical Product is a pharmaceutically equivalent product that may or may not be therapeutically equivalent or bioequivalent. Generic pharmaceutical products that are therapeutically equivalent are interchangeable.

High solubility: A Pharmaceutical product is classified as highly soluble if the highest therapeutic dose of the pharmaceutical product is completely soluble in 250 mL or less of solvent over the pH range of 1.2-6.8 at 37 ± 1°C, that is (i.e.), DSV ≤ 250 mL over the pH range.

Highest dose - highest approved therapeutic dose for the pharmaceutical product in PPB. If not currently approved in PPB, the highest proposed dose is applicable.

Low absorption: less than (<) 85% of the administered dose absorbed.

Low solubility: A Pharmaceutical product is classified as a low solubility compound if the highest therapeutic dose of the pharmaceutical product is not completely soluble in 250 mL of solvent at any pH within the pH range of 1.2-6.8 at 37 ± 1°C, i.e., DSV greater than (>) 250 mL at any pH within the range.

Metabonate - a substance which appears to be a metabolite but is actually an artefact formed during experimental conditions [for example (e.g.), isolation and storage].

Pharmaceutical alternatives: Pharmaceutical products are pharmaceutical alternatives if they contain the same active moiety but differ either in chemical form (e.g. salt, ester) of that moiety or in the dosage form or strength, administered by the same route of administration but are otherwise not pharmaceutically equivalent. Pharmaceutical alternatives do not necessarily imply bioequivalence.

Pharmaceutical Dosage Form: A pharmaceutical dosage form is the form of the completed pharmaceutical product e.g. tablet, capsule, injection, elixir, suppository.

Pharmaceutical Equivalence: Pharmaceutical products are pharmaceutically equivalent if they contain the same amount of the same API(s) in the same dosage form, if they meet the same or comparable standards and if they are intended to be administered by the same route. Pharmaceutical equivalence does not necessarily imply bioequivalence as differences in the excipients and/or the manufacturing process can lead to changes in dissolution and/or absorption.

Pharmaceutical Product: Any preparation for human (or animal) use, containing one or more APIs with or without pharmaceutical excipients or additives, that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

Proportionally Similar Dosage Forms/Products: Pharmaceutical products are considered proportionally similar in the following cases:

Rapidly dissolving product - a product in which not less than 85% of the labelled amount is released within 30 minutes or less during a product dissolution test under the conditions specified in these guidelines.

Solution - a homogeneous mixture in a single phase with no precipitate.

Therapeutic Equivalence: Two pharmaceutical products are therapeutically equivalent if they are pharmaceutically equivalent or are pharmaceutical alternatives and, after administration in the same molar dose, their effects with respect to both efficacy and safety are essentially the same, as determined from appropriate bioequivalence, pharmacodynamic, clinical or *in vitro* studies.

Very rapidly dissolving product - not less than 85% of the labelled amount is released within 15 minutes or less during a product dissolution test under the conditions specified in this guideline.

1. INTRODUCTION

The objective of this guideline is to specify the requirements for the design, conduct, and evaluation of bioequivalence studies for immediate release and modified release dosage forms with systemic action.

Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailability (rate and extent) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable *in vivo* performance, i.e. similarity in terms of safety and efficacy.

In bioequivalence studies, the plasma concentration time curve is generally used to assess the rate and extent of absorption. Selected pharmacokinetic parameters and pre-set acceptance limits allow the final decision on bioequivalence of the tested products. The absorption rate of a drug is influenced by pharmacokinetic parameters like AUC, the area under the concentration time curve, reflects the extent of exposure, C_{max}, the maximum plasma concentration or peak exposure, and the time to maximum plasma concentration, t_{max}. In applications for generic medicinal products to the PPB, the concept of bioequivalence is fundamental.

The purpose of establishing bioequivalence is to demonstrate equivalence in biopharmaceutics quality between the generic medicinal product and a comparator medicinal product in order to allow bridging of preclinical tests and of clinical trials associated with the comparator medicinal product. The definition for generic medicinal products is a product that has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the comparator medicinal product, and whose bioequivalence with the comparator medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. Furthermore, the various immediate-release oral pharmaceutical forms shall

be considered to be one and the same pharmaceutical form. Other types of applications may also require demonstration of bioequivalence, including variations, fixed combinations, extensions and generic applications.

The recommendations on design and conduct given for bioequivalence studies in this guideline may also be applied to comparative bioavailability studies evaluating different formulations used during the development of a new medicinal product containing a new chemical entity and to comparative bioavailability studies included in extension or generic applications that are not based exclusively on bioequivalence data.

Generally, results from comparative bioavailability studies should be provided in support of the safety and efficacy of each proposed product and of each proposed strength included in the submission. In the absence of such studies, a justification supporting a waiver of this requirement should be provided in this section for each product and each strength. For example, if there are several strengths of the proposed product, and comparative bioavailability data has not been submitted for all strengths, the applicant should provide a scientific justification for not conducting studies on each strength. This justification may address issues such as the nature of the kinetics of the drug (e.g., linear versus non-linear), and the proportionality of the strengths for which a waiver is sought to the strength on which a comparative bioavailability study was conducted.

The statement of justification for waiver will include supporting data (e.g. comparative dissolution data) which should be provided in the relevant module(s) of the CTD submission (i.e., Modules 2-5). For example, comparative dissolution profiles should be provided in Module 3, Section 3.2.P.2 of the main PPB Guidelines on Documentation for Application of Human Pharmaceutical Products (Pharmaceutical Development).

1.2 Scope

This guideline focuses on recommendations for bioequivalence studies for immediate release formulations and modified release with systemic action. The scope is limited to chemical entities. Biological products are not covered by these guidelines.

In case bioequivalence cannot be demonstrated using drug concentrations, in exceptional circumstances pharmacodynamic or clinical endpoints may be needed.

2. Exemptions for carrying out bioequivalence studies

Omission of BE studies must be justified except if a product fulfils one or more of the following conditions: -

a) Solutions, complex or simple, which do not contain any ingredient which can be regarded as a pharmacologically active substance;
b) Simple aqueous solutions intended for intravenous injection or infusion containing the same active substance(s) in the same concentration as currently registered products. Simple solutions do not include complex solution such as micellar or liposomal solutions;
c) Solutions for injection that contain the same active ingredients and excipients in the same concentrations as currently registered products and which are administered by the same route(s);
d) Products that are powder for reconstitution as a solution and the solution meets either criterion (b) or (c) above;
e) Oral immediate release tablets, capsules and suspensions containing active pharmaceutical ingredients eligible for BCS based biowaivers.
f) Oral solutions containing the same active ingredient(s) in the same concentration as a currently registered or innovator oral solution and not containing excipients that may significantly affect gastric passage or absorption of the active ingredient(s);
g) Products for topical use provided the product is intended to act without systemic absorption when applied locally;
h) Products containing therapeutic substances, which are not systemically or locally absorbed i.e. an oral dosage form which is not intended to be absorbed (e.g., barium sulphate enemas, Antacid, Radioopaque Contrast Media, or powders in which no ingredient is absorbed etc.). If there is doubt as to whether absorption occurs, a study or justification may be required;

i) Otic or ophthalmic products prepared as aqueous solutions and containing the same active pharmaceutical ingredient(s) in the same concentration;
j) The product is an oral solution, syrup, or other similarly solubilized form;
k) The product is oro-dispersable product is eligible for a biowaiver application only if there is no buccal or sublingual absorption and the product is labelled to be consumed with water;
l) The product is an inhalant volatile anaesthetic solution, Inhalation and nasal preparations;
m) The product is a reformulated product by the original manufacturer that is identical to the original product except for colouring agents, flavouring agents or preservatives, which are recognized as having no influence upon bioavailability;

Gases;

3. Design, conduct and evaluation of bioequivalence studies

3.1 Study Design, conduct and evaluation of bioequivalence studies

The design, conduct and evaluation of the Bioequivalence study should comply with ICH GCP requirements (E6).

In the following sections, requirements for the design and conduct of comparative bioavailability studies are formulated. Investigator(s) should have appropriate expertise, qualifications and competence to undertake a proposed study and is familiar with pharmacokinetic theories underlying bioavailability studies. The design should be based on a reasonable knowledge of the pharmacodynamics and/or the pharmacokinetics of the active substance in question.

The number of studies and study design depend on the physico-chemical characteristics of the substance, its pharmacokinetic properties and proportionality in composition, and should be justified accordingly. In particular it may be necessary to address the linearity of pharmacokinetics, the need for studies both in fed and fasting state, the need for enantioselective analysis and the possibility of waiver for additional strengths (see Sections 3.1.4, 3.1.5 and 3.1.6).

Module 2.7.1 should list all relevant studies carried out with the product applied for, i.e. bioequivalence studies comparing the formulation applied for (i.e. same composition and manufacturing process) with a Comparator medicinal product approved by PPB. Studies should be included in the list regardless of the study outcome. Full study reports should be provided for all studies, except pilot studies for which study report synopses (in accordance with ICH E3) are sufficient. Full study reports for pilot studies should be available upon request. Study report synopses for bioequivalence or comparative bioavailability studies conducted during formulation development should also be included in Module 2.7. Bioequivalence studies comparing the product applied for with non-PPB Comparator products should not be submitted and do not need to be included in the list of studies.

3.1.1 Study design

Standard design

If two formulations are compared, a randomised, two-period, two-sequence single dose crossover design is recommended. The treatment periods should be separated by a wash out period sufficient to ensure that drug concentrations are below the lower limit of bioanalytical quantification in all subjects at the beginning of the second period. Normally at least 5 elimination half-lives are necessary to achieve this. The study should be designed in such a way that the treatment effect (formulation effect) can be distinguished from other effects. In order to reduce variability a cross over design usually is the first choice.

Alternative designs

Under certain circumstances, provided the study design and the statistical analyses are scientifically sound, alternative well-established designs could be considered such as parallel design for substances with very long half -life and replicate designs e.g. for substances with highly variable pharmacokinetic characteristics (see Section 3.1.10). The study should be designed in such a way that the formulation effect can be distinguished from other effects.

Other designs or methods may be chosen in specific situations, but should be

fully justified in the protocol and final study report. The subjects should be allocated to treatment sequences in a randomised order. In general, single dose studies will suffice, but there are situations in which steady-state studies may be required:

a) If problems of sensitivity preclude sufficiently precise plasma concentration measurement after single dose;

b) If the intra-individual variability in the plasma concentrations or disposition rate is inherently large;

c) In the case of dose-or time-dependent pharmacokinetics

d) In the case of extended-release products (in addition to single dose studies)

e) In such steady-state studies, the administration scheme should follow the usual dosage recommendations.

In such steady-state studies, the administration scheme should follow the usual dosage recommendations.

Conduct of a multiple dose study in patients is acceptable if a single dose study cannot be conducted in healthy volunteers due to tolerability reasons, and a single dose study is not feasible in patients.

In the rare situation where problems of sensitivity of the analytical method preclude sufficiently precise plasma concentration measurements after single dose administration and where the concentrations at steady state are sufficiently high to be reliably measured, a multiple dose study may be acceptable as an alternative to the single dose study. However, given that a multiple dose study is less sensitive in detecting differences in C_{max}, this will only be acceptable if the applicant can adequately justify that the sensitivity of the analytical method cannot be improved and that it is not possible to reliably measure the parent compound after single dose administration taking into account also the option of using a supra-therapeutic dose in the bioequivalence study (see also Section 3.1.6). Due to the recent development in the bioanalytical methodology, it is unusual that parent drug cannot be measured accurately and precisely. Hence, use of a multiple dose study instead of a single dose study, due to limited sensitivity of the analytical method, will only be

accepted in exceptional cases.

In steady-state studies, the washout period of the previous treatment can overlap with the build-up of the second treatment, provided the build-up period is sufficiently long (at least 5 times the terminal half-life).

3.1.2 Comparator and test products

Comparator Product

Test products in an application for a generic product or an extension of a generic product are normally compared with the corresponding dosage form of a comparator medicinal product, if available on the market. The product used as a comparator product in the bioequivalence study should meet the criteria stipulated in Annex XIV.

In an application for extension of a medicinal product which has been initially approved by PPB and when there are several dosage forms of this medicinal product on the market, it is recommended that the dosage form used for the initial approval of the concerned medicinal product (and which was used in clinical efficacy and safety studies) is used as comparator product, if available on the market.

The selection of the Comparator product used in a bioequivalence study should be based on assay content and dissolution data and is the responsibility of the Applicant. Unless otherwise justified, the assayed content of the batch used as test product should not differ more than 5% from that of the batch used as comparator product determined with the test procedure proposed for routine quality testing of the test product. The Applicant should document how a representative batch of the comparator product with regards to dissolution and assay content has been selected. It is advisable to investigate more than one single batch of the Comparator product when selecting the Comparator product batch for the bioequivalence study. (to be removed and moved to the guideline on comparator).

Test product

The test product used in the study should be representative of the product to

be marketed and this should be discussed and justified by the applicant. For example, for oral solid forms for systemic action:

a) The test product should usually originate from a batch of at least 1/10 of production scale or 100,000 units, whichever is greater, unless otherwise justified.

b) The production of batches used should provide a high level of assurance that the product and process will be feasible on an industrial scale. In case of a production batch smaller than 100,000 units, a full production batch will be required.

c) The characterization and specification of critical quality attributes of the finished pharmaceutical product, such as dissolution, should be established from the test batch, i.e. the clinical batch for which bioequivalence has been demonstrated.

d) Samples of the product from additional pilot and/or full-scale production batches, submitted to support the application, should be compared with those of the bioequivalence study test batch, and should show similar in vitro dissolution profiles when employing suitable dissolution test conditions.

Comparative dissolution profile testing should be undertaken on the first three production batches.

If full scale production batches are not available at the time of submission, the applicant should not market a batch until comparative dissolution profile testing has been completed.

The results should be provided at the PPB's request or if the dissolution profiles are not similar together with proposed action to be taken.

For other immediate release pharmaceutical forms for systemic action, justification of the representative nature of the test batch should be similarly established.

Impact of excipients

Identify any excipients present in either product that are known to impact on *in vivo* absorption processes. Provide a literature-based summary of the mechanism by which these effects are known to occur should be included and relevant full discussion enclosed, if applicable.

Comparative qualitative and quantitative differences between the compositions of the test and comparator products

Identify all qualitative (and quantitative, if available) differences between the compositions of the test and comparator products. The data obtained and methods used for the determination of the quantitative composition of the comparator product as required by the guidance documents should be summarized here for assessment.

Impact of the differences between the compositions of the test and comparator products

Provide a detailed comment on the impact of any differences between the compositions of the test and comparator products with respect to drug release and in vivo absorption

Packaging of study products

The comparator and test products should be packed in an individual way for each subject and period, either before their shipment to the trial site, or at the trial site itself. Packaging (including labelling) should be performed in accordance with good manufacturing practice.

It should be possible to identify unequivocally the identity of the product administered to each subject at each trial period. Packaging, labelling and administration of the products to the subjects should therefore be documented in detail. This documentation should include all precautions taken to avoid and identify potential dosing mistakes. The use of labels with a tear-off portion is recommended.

3.1.3 Subjects

Number of subjects

The number of subjects to be included in the study should be based on an appropriate sample size calculation. The number of evaluable subjects in a bioequivalence study should not be less than 12.

The number of subjects should be determined using appropriate methods taking into account the error variance associated with the primary parameters to be studied (as estimated for a pilot experiment, from previous studies or from published data), the significance level desired and the deviation from the comparator product compatible with bioequivalence (± 20%) and compatible with safety and efficacy. For a parallel design study a greater number of subjects may be required to achieve sufficient study power.

Applicants should enter a sufficient number of subjects in the study to allow for dropouts. Because replacement of subjects could complicate the statistical model and analysis, dropouts generally should not be replaced.

Selection of subjects

The subject population for bioequivalence studies should be selected with the aim of permitting detection of differences between pharmaceutical products. The subject population for bioequivalence studies should be selected with the aim to minimise variability and permit detection of differences between pharmaceutical products. In order to reduce variability not related to differences between products, the studies should normally be performed in healthy volunteers unless the drug carries safety concerns that make this unethical. This model, *in vivo* healthy volunteers, is regarded as adequate in most instances to detect formulation differences and to allow extrapolation of the results to populations for which the comparator medicinal product is approved (the elderly, children, patients with renal or liver impairment, etc.).

The inclusion/exclusion criteria should be clearly stated in the protocol. Subjects to be enrolled in a crossover bioequivalence study should be between18-50years in age, preferably have a Body Mass Index between 18.5 and 30 kg/m^2.

The subjects should be screened for suitability by means of clinical laboratory tests, a medical history, and a physical examination. Depending on the drug's therapeutic class and safety profile, special medical investigations and precautions may have to be carried out before, during and after the completion of the study.

Subjects could belong to either sex; however, the risk to women of childbearing potential should be considered. Subjects should preferably be non -smokers and without a history of alcohol or drug abuse. Phenotyping and/or genotyping of subjects may be considered for safety or pharmacokinetic reasons.

In parallel design studies, the treatment groups should be comparable in all known variables that may affect the pharmacokinetics of the active substance (e.g. age, body weight, sex, ethnic origin, smoking status, extensive/poor metabolic status). This is an essential prerequisite to give validity to the results from such studies.

Inclusion of patients

If the investigated active substance is known to have adverse effects and the pharmacological effects or risks are considered unacceptable for healthy volunteers, it may be necessary to include patients instead, under suitable precautions and supervision. In this case the applicant should justify the alternative.

3.1.4 Study conduct

Standardisation of the bioequivalence studies

The test conditions should be standardized in order to minimize the variability of all factors involved except that of the products being tested. Therefore, it is recommended to standardize diet, fluid intake and exercise.

The time of day for ingestion should be specified. Subjects should fast for at least 8 hours prior to administration of the products, unless otherwise justified. As fluid intake may influence gastric passage for oral administration forms, the test and comparator products should be administered with a standardized volume of fluid (at least 150 ml). It is recommended that water is allowed as

desired except for one hour before and one hour after drug administration and no food is allowed for at least 4 hours post-dose. Meals taken after dosing should be standardized in regard to composition and time of administration during an adequate period of time (e.g. 12 hours).

In case the study is to be performed during fed conditions, the timing of administration of the finished pharmaceutical product in relation to food intake is recommended to be according to the SmPC of the originator product. If no specific recommendation is given in the originator SmPC, it is recommended that subjects should start the meal 30 minutes prior to administration of the finished pharmaceutical product and eat this meal within 30 minutes.

As the bioavailability of an active moiety from a dosage form could be dependent upon gastrointestinal transit times and regional blood flows, posture and physical activity may need to be standardized.

The subjects should abstain from food and drinks, which may interact with circulatory, gastrointestinal, hepatic or renal function (e.g. alcoholic drinks or certain fruit juices such as grapefruit juice) during a suitable period before and during the study. Subjects should not take any other concomitant medication (including herbal remedies) for an appropriate interval before as well as during the study. Contraceptives are, however, allowed. In case concomitant medication is unavoidable and a subject is administered other drugs, for instance to treat adverse events like headache, the use must be reported (dose and time of administration) and possible effects on the study outcome must be addressed. In rare cases, the use of a concomitant medication is needed for all subjects for safety or tolerability reasons (e.g. opioid antagonists, anti -emetics). In that scenario, the risk for a potential interaction or bioanalytical interference affecting the results must be addressed.

Medicinal products that according to the originator SmPC are to be used explicitly in combination with another product (e.g. certain protease inhibitors in combination with ritonavir) may be studied either as the approved combination or without the product recommended to be administered concomitantly.

In bioequivalence studies of endogenous substances, factors that may influence the endogenous baseline levels should be controlled if possible (e.g. strict control of dietary intake).

Sampling times

Several samples of appropriate biological matrix (blood, plasma/serum, urine) are collected at various time intervals post-dose. The sampling schedule depends on the pharmacokinetic characteristics of the drug being tested. In most cases, plasma or serum is the matrix of choice. However, if the parent drug is not metabolized and is largely excreted unchanged and can be suitably assayed in the urine, urinary drug levels may be used to assess bioequivalence, if plasma/serum concentrations of the drug cannot be reliably measured.

A sufficient number of samples are collected during the absorption phase to adequately describe the plasma concentration-time profile. The sampling schedule should include frequent sampling around predicted T_{max} to provide a reliable estimate of peak exposure. Intensive sampling is carried out around the time of the expected peak concentration. In particular, the sampling schedule should be planned to avoid C_{max} being the first point of a concentration time curve. The sampling schedule should also cover the plasma concentration time curve long enough to provide a reliable estimate of the extent of exposure which is achieved if $AUC_{(0-t)}$ covers at least 80% of $AUC_{(0-\infty)}$. At least three to four samples are needed during the terminal log-linear phase in order to reliably estimate the terminal rate constant (which is needed for a reliable estimate of $AUC_{(0-\infty)}$. AUC truncated at 72 h [$AUC_{(0-72h)}$] may be used as an alternative to $AUC_{(0-t)}$ for comparison of extent of exposure as the absorption phase has been covered by 72 h for immediate release formulations. A sampling period longer than 72 h is therefore not considered necessary for any immediate release formulation irrespective of the half-life of the drug. Sufficient numbers of samples should also be collected in the log-linear elimination phase of the drug so that the terminal elimination rate constant and half-life of the drug can be accurately determined. A sampling period extending to at least five terminal elimination half-lives of the drug or five the longest half-life of the pertinent analyte (if more than one analyte) is usually sufficient. The samples are

appropriately processed and stored carefully under conditions that preserve the integrity of the analyte(s).

In multiple -dose studies, the pre-dose sample should be taken immediately before (within 5 minutes) dosing and the last sample is recommended to be taken within 10 minutes of the nominal time for the dosage interval to ensure an accurate determination of $AUC_{(0-\tau)}$.

If urine is used as the biological sampling fluid, urine should normally be collected over no less than three times the terminal elimination half-life. However, in line with the recommendations on plasma sampling, urine does not need to be collected for more than 72 h. If rate of excretion is to be determined, the collection intervals need to be as short as feasible during the absorption phase (see also Section 3.1.5).

For endogenous substances, the sampling schedule should allow characterization of the endogenous baseline profile for each subject in each period. Often, a baseline is determined from 2-3 samples taken before the finished pharmaceutical products are administered. In other cases, sampling at regular intervals throughout 1-2 day(s) prior to administration may be necessary in order to account for fluctuations in the endogenous baseline due to circadian rhythms (see Section 3.1.5).

Washout period

Subsequent treatments should be separated by periods long enough to eliminate the previous dose before the next one (wash-out period). In steady-state studies wash-out of the last dose of the previous treatment can overlap with the build-up of the second treatment, provided the build-up period is sufficiently long (at least five(5) times the dominating half-life).

Fasting or fed conditions

In general, a bioequivalence study should be conducted under fasting conditions as this is considered to be the most sensitive condition to detect a potential difference between formulations. For products where the SmPC recommends intake of the innovator medicinal product on an empty stomach or irrespective of food intake, the bioequivalence study should hence be

conducted under fasting conditions. For products where the SmPC recommends intake of the innovator medicinal product only in fed state, the bioequivalence study should generally be conducted under fed conditions.

However, for products with specific formulation characteristics (e.g. microemulsions, prolonged modified release, solid dispersions), bioequivalence studies performed under both fasted and fed conditions are required unless the product must be taken only in the fasted state or only in the fed state.

In cases where information is required in both the fed and fasted states, it is acceptable to conduct either two separate two-way cross-over studies or a four-way cross-over study.

In studies performed under fed conditions, the composition of the meal is recommended to be according to the SmPC of the originator product. If no specific recommendation is given in the originator SmPC, the meal should be a high-fat (approximately 50 percent of total caloric content of the meal) and high -calorie (approximately 800 to 1000 kcal) meal. This test meal should derive approximately 150, 250, and 500-600 kcal from protein, carbohydrate, and fat, respectively. The composition of the meal should be described with regard to protein, carbohydrate and fat content (specified in grams, calories and relative caloric content (%).

3.1.5 Characteristics to be investigated

Pharmacokinetic parameters (Bioavailability Metrics)

In bioavailability studies, the shape and area under the plasma concentration versus time curves are mostly used to assess rate (Cmax, tmax) and extent (AUC) of exposure. Sampling points or periods should be chosen such that the concentration versus time profile is sufficiently defined to allow calculation of relevant parameters.

For single-dose studies, the following parameters should be measured or calculated:

a) Area under the plasma, serum or blood concentration–time curve from time zero to time *t* (AUC0–*t*), where *t* is the last sampling time-point with a measurable concentration of the API in the individual formulation tested.

The method of calculating AUC values should be specified. Non-compartmental methods should be used for pharmacokinetic calculations in bioequivalence studies;

b) C_{max} is the maximum or peak concentration observed representing peak exposure of API (or metabolite) in plasma, serum or whole blood.

Usually AUC0–*t* and C_{max} are considered to be the most relevant parameters for assessment of bioequivalence. In addition, it is recommended that the following parameters be estimated:

a) area under the plasma, serum or blood concentration–time curve from time zero to time infinity (AUC0–∞) representing total exposure, where AUC0–∞ = AUC0–*t* + Clast /Ke; Clast is the last measurable analyte concentration and Ke is the terminal or elimination rate constant calculated according to an appropriate method;

b) t_{max} is the time after administration of the FPP at which Cmax is observed.

For additional information the elimination parameters can be calculated:

- T1/2 is the plasma (serum, whole blood) half-life.

For multiple-dose studies conducted with modified-release products, the following parameters should be calculated:

- AUCτ is AUC over one dosing interval (τ) at steady state;
- Cmax ;
- Cmin (Ctau) is concentration at the end of a dosing interval;
- peak trough fluctuation is percentage difference between Cmax and Cmin.

As release mechanisms of pharmaceutical products become more complex, e.g. products with an immediate-release and a modified-release component, additional parameters such as partial AUC measures may be necessary to ensure the bioequivalence of two products. When urine samples are used,

cumulative urinary recovery (Ae) and maximum urinary excretion rate are employed instead of AUC and Cmax.

Parent compound or metabolites

In principle, evaluation of bioequivalence should be based upon measured concentrations of the parent compound. The reason for this is that C_{max} of a parent compound is usually more sensitive to detect differences between formulations in absorption rate than C_{max} of a metabolite.

Inactive pro-drugs

Further, for inactive pro-drugs, demonstration of bioequivalence for parent compound is recommended. The active metabolite does not need to be measured. However, some pro-drugs may have low plasma concentrations and be quickly eliminated resulting in difficulties in demonstrating bioequivalence for parent compounds. In this situation it is acceptable to demonstrate bioequivalence for the main active metabolite without measurement of parent compound. In the context of this guideline, a parent compound can be considered to be an inactive pro-drug if it has no or very low contribution to clinical efficacy.

Use of metabolite data as surrogate for active parent compound

The use of a metabolite as a surrogate for an active parent compound is not encouraged. This can only be considered if the applicant can adequately justify that the sensitivity of the analytical method for measurement of the parent compound cannot be improved and that it is not possible to reliably measure the parent compound after single dose administration taking into account also the option of using a higher single dose in the bioequivalence study. Due to recent developments in bioanalytical methodology, it is unusual that parent drugs cannot be measured accurately and precisely. Hence, the use of a metabolite as a surrogate for active parent compound is expected to be accepted only in exceptional cases. When using metabolite data as a substitute for active parent drug concentrations, the applicant should present any available data supporting the view that the metabolite exposure will reflect the parent drug and that the metabolite formation is not saturated at therapeutic doses.

Enantiomers

The use of achiral bioanalytical methods is generally acceptable. However, the individual enantiomers should be measured when all the following conditions are met:

a) the enantiomers exhibit different pharmacokinetics;

b) the enantiomers exhibit pronounced difference in pharmacodynamics;

c) the exposure (AUC) ratio of enantiomers is modified by a difference in the rate of absorption.

The individual enantiomers should also be measured if the above conditions are fulfilled or are unknown. If one enantiomer is pharmacologically active and the other is inactive or has a low contribution to activity, it is sufficient to demonstrate bioequivalence for the active enantiomer.

The use of urinary data

If drug/API concentrations in blood are too low to be detected and a substantial amount (> 40 %) of the drug/API is eliminated unchanged in the urine, then urine may serve as the biological fluid to be sampled.

If a reliable plasma C_{max} can be determined, this should be combined with urinary data on the extent of exposure for assessing bioequivalence. When using urinary data, the applicant should present any available data supporting that urinary excretion will reflect plasma exposure.

When urine is collected:

a) The volume of each sample should be measured immediately after collection and included in the report.

b) Urine should be collected over an extended period and generally no less than seven times the terminal elimination half-life, so that the amount excreted to infinity (Ae_{∞}) can be estimated.

c) Sufficient samples should be obtained to permit an estimate of the rate and extent of renal excretion. For a 24-hour study, sampling times of 0 to 2, 2 to 4, 4 to 8, 8 to 12, and 12 to 24 hours post-dose are usually

appropriate.

d) The actual clock time when samples are collected, as well as the elapsed time relative to API administration, should be recorded.

Urinary Excretion Profiles: -

In the case of API's predominantly excreted renally, the use of urine excretion data may be advantageous in determining the extent of drug/API input. However, justification should also be given when this data is used to estimate the rate of absorption.

Sampling points should be chosen so that the cumulative urinary excretion profiles can be defined adequately so as to allow accurate estimation of relevant parameters.

The following bioavailability parameters are to be estimated: -

a) Ae_t, Ae_∞as appropriate for urinary excretion studies

b) Any other justifiable characteristics.

c) The method of estimating AUC-values should be specified.

Endogenous substances

If the substance being studied is endogenous, the calculation of pharmacokinetic parameters should be performed using baseline correction so that the calculated pharmacokinetic parameters refer to the additional concentrations provided by the treatment. Administration of supra -therapeutic doses can be considered in bioequivalence studies of endogenous drugs, provided that the dose is well tolerated, so that the additional concentrations over baseline provided by the treatment may be reliably determined. If a separation in exposure following administration of different doses of a particular endogenous substance has not been previously established this should be demonstrated, either in a pilot study or as part of the pivotal bioequivalence study using different doses of the comparator formulation, in order to ensure that the dose used for the bioequivalence comparison is sensitive to detect potential differences between formulations.

The exact method for baseline correction should be pre-specified and justified

in the study protocol. In general, the standard subtractive baseline correction method, meaning either subtraction of the mean of individual endogenous pre-dose concentrations or subtraction of the individual endogenous pre-dose AUC, is preferred. In rare cases where substantial increases over baseline endogenous levels are seen, baseline correction may not be needed.

In bioequivalence studies with endogenous substances, it cannot be directly assessed whether carry-over has occurred, so extra care should be taken to ensure that the washout period is of an adequate duration.

3.1.6 Strength to be investigated

If several strengths of a test product are applied for, it may be sufficient to establish bioequivalence at only one or two strengths, depending on the proportionality in composition between the different strengths and other product related issues described below. The strength(s) to evaluate depends on the linearity in pharmacokinetics of the active substance.

In case of non-linear pharmacokinetics (i.e. not proportional increase in AUC with increased dose) there may be a difference between different strengths in the sensitivity to detect potential differences between formulations. In the context of this guideline, pharmacokinetics is considered to be linear if the difference in dose-adjusted mean AUCs is no more than 25% when comparing the studied strength (or strength in the planned bioequivalence study) and the strength(s) for which a waiver is considered. In order to assess linearity, the applicant should consider all data available in the public domain with regard to the dose proportionality and review the data critically. Assessment of linearity will consider whether differences in dose-adjusted AUC meet a criterion of ± 25%.

If bioequivalence has been demonstrated at the strength(s) that are most sensitive to detect a potential difference between products, in vivo bioequivalence studies for the other strength(s) can be waived.

General biowaiver criteria

The following general requirements must be met where a waiver for additional strength(s) is claimed: -

a) the pharmaceutical products are manufactured by the same manufacturing process,

b) the qualitative composition of the different strengths is the same,

c) the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),

   If there is some deviation from quantitatively proportional composition, condition c is still considered fulfilled if condition i) and ii) or i) and iii) below apply to the strength used in the bioequivalence study and the strength(s) for which a waiver is considered: -

   i. the amount of the active substance(s) is less than 5 % of the tablet core weight, the weight of the capsule content.

   ii. the amounts of the different core excipients or capsule content are the same for the concerned strengths and only the amount of active substance is changed.

   iii. the amount of a filler is changed to account for the change in amount of active substance. The amounts of other core excipients or capsule content should be the same for the concerned strengths.

d) An appropriate in vitro dissolution data should confirm the adequacy of waiving additional in vivo bioequivalence testing (see Section 3.2).

Linear pharmacokinetics

For products where all the above conditions a) to d) are fulfilled, it is sufficient to establish bioequivalence with only one strength.

The bioequivalence study should in general be conducted at the highest strength. For products with linear pharmacokinetics and where the active pharmaceutical ingredient is highly soluble based on BCS Biowaiver, selection of a lower strength than the highest is also acceptable. Selection of a lower strength may also be justified if the highest strength cannot be administered to

healthy volunteers for safety/tolerability reasons. Further, if problems of sensitivity of the analytical method preclude sufficiently precise plasma concentration measurements after single dose administration of the highest strength, a higher dose may be selected (preferably using multiple tablets of the highest strength). The selected dose may be higher than the highest therapeutic dose provided that this single dose is well tolerated in healthy volunteers and that there are no absorption or solubility limitations at this dose.

Non-linear pharmacokinetics

For drugs with non-linear pharmacokinetics characterized by a more than proportional increase in AUC with increasing dose over the therapeutic dose range, the bioequivalence study should in general be conducted at the highest strength. As for drugs with linear pharmacokinetics a lower strength may be justified if the highest strength cannot be administered to healthy volunteers for safety/tolerability reasons. Likewise, a higher dose may be used in case of sensitivity problems of the analytical method in line with the recommendations given for products with linear pharmacokinetics above.

For drugs with a less than proportional increase in AUC with increasing dose over the therapeutic dose range, bioequivalence should in most cases be established both at the highest strength and at the lowest strength (or strength in the linear range), i.e. in this situation two bioequivalence studies are needed. If the non-linearity is not caused by limited solubility but is due to e.g. saturation of uptake transporters and provided that conditions a) to d) above are fulfilled and the test and comparator products do not contain any excipients that may affect gastrointestinal motility or transport proteins, it is sufficient to demonstrate bioequivalence at the lowest strength (or a strength in the linear range).

Selection of other strengths may be justified if there are analytical sensitivity problems preventing a study at the lowest strength or if the highest strength cannot be administered to healthy volunteers for safety/tolerability reasons.

Bracketing approach

Where bioequivalence assessment at more than two strengths is needed, e.g.

because of deviation from proportional composition, a bracketing approach may be used. In this situation it can be acceptable to conduct two bioequivalence studies, if the strengths selected represent the extremes, e.g. the highest and the lowest strength or the two strengths differing most in composition, so that any differences in composition in the remaining strengths is covered by the two conducted studies.

Where bioequivalence assessment is needed both in fasting and in fed state and at two strengths due to nonlinear absorption or deviation from proportional composition, it may be sufficient to assess bioequivalence in both fasting and fed state at only one of the strengths. Waiver of either the fasting or the fed study at the other strength(s) may be justified based on previous knowledge and/or pharmacokinetic data from the study conducted at the strength tested in both fasted and fed state. The condition selected (fasting or fed) to test the other strength(s) should be the one which is most sensitive to detect a difference between products.

Fixed combinations

The conditions regarding proportional composition should be fulfilled for all active substances of fixed combinations. When considering the amount of each active substance in a fixed combination the other active substance(s) can be considered as excipients. In the case of bilayer tablets, each layer may be considered independently.

3.1.7 Bioanalytical methodology

The bioanalysis of bioequivalence samples should be performed in accordance with the principles of Good Laboratory Practice (GLP). However, as human bioanalytical studies fall outside the scope of GLP, the sites conducting the studies are not required to be monitored as part of a national GLP compliance programme.

The bioanalytical methods used to determine the active principle and/or its biotransformation products in plasma, serum, blood or urine or any other suitable matrix must be well characterised, fully validated and documented to yield reliable results that can be satisfactorily interpreted. Within study

validation should be performed using Quality control samples in each analytical run.

The main objective of method validation is to demonstrate the reliability of a particular method for the quantitative determination of analyte(s) concentration in a specific biological matrix.The main characteristics of a bioanalytical method that is essential to ensure the acceptability of the performance and the reliability of analytical results includes but not limited to: selectivity, sensitivity, lower limit of quantitation, the response function (calibration curve performance), accuracy, precision and stability of the analyte(s) in the biological matrix under processing conditions and during the entire period of storage.

The lower limit of quantitation should be 1/20 of C_{max} or lower, as pre-dose concentrations should be detectable at 5% of C_{max} or lower (see Section 3.1.8 *Carry-over effects*).

Reanalysis of study samples should be predefined in the study protocol (and/or SOP) before the actual start of the analysis of the samples. Normally reanalysis of subject samples because of a pharmacokinetic reason is not acceptable. This is especially important for bioequivalence studies, as this may bias the outcome of such a study.

Analysis of samples should be conducted without information on treatment.

The validation report of the bioanalytical method should be included in Module 5 of the application.

3.1.8 Evaluation

In bioequivalence studies, the pharmacokinetic parameters should in general not be adjusted for differences in assayed content of the test and comparator batch. However, in exceptional cases where a comparator batch with an assay content differing less than 5% from test product cannot be found (see Section 3.1.2 on Comparator and test product) content correction could be accepted. If content correction is to be used, this should be pre-specified in the protocol and justified by inclusion of the results from the assay of the test and comparator products in the protocol.

Subject accountability

Ideally, all treated subjects should be included in the statistical analysis. However, subjects in a crossover trial who do not provide valuable data for both of the test and comparator products (or who fail to provide valuable data for the single period in a parallel group trial) should not be included.

The data from all treated subjects should be treated equally. It is not acceptable to have a protocol which specifies that 'spare' subjects will be included in the analysis only if needed as replacements for other subjects who have been excluded. It should be planned that all treated subjects should be included in the analysis, even if there are no drop-outs.

In studies with more than two treatment arms (e.g. a three period study including two comparators, one from EU and another from USA, or a four period study including test and comparator in fed and fasted states), the analysis for each comparison should be conducted excluding the data from the treatments that are not relevant for the comparison in question.

Reasons for exclusion

Unbiased assessment of results from randomised studies requires that all subjects are observed and treated according to the same rules. These rules should be independent from treatment or outcome. In consequence, the decision to exclude a subject from the statistical analysis must be made before bioanalysis.

In principle any reason for exclusion is valid provided it is specified in the protocol and the decision to exclude is made before bioanalysis. However the exclusion of data should be avoided, as the power of the study will be reduced and a minimum of 12 evaluable subjects is required.

Examples of reasons to exclude the results from a subject in a particular period are events such as vomiting and diarrhoea which could render the plasma concentration-time profile unreliable. In exceptional cases, the use of concomitant medication could be a reason for excluding a subject.

The permitted reasons for exclusion must be pre-specified in the protocol. If one of these events occurs it should be noted in the CRF as the study is being conducted. Exclusion of subjects based on these pre-specified criteria should

be clearly described and listed in the study report.

Exclusion of data cannot be accepted on the basis of statistical analysis or for pharmacokinetic reasons alone, because it is impossible to distinguish the formulation effects from other effects influencing the pharmacokinetics.

The exceptions to this are: -

a) A subject with lack of any measurable concentrations or only very low plasma concentrations for comparator medicinal product. A subject is considered to have very low plasma concentrations if its AUC is less than 5% of comparator medicinal product geometric mean AUC (which should be calculated without inclusion of data from the outlying subject). The exclusion of data due to this reason will only be accepted in exceptional cases and may question the validity of the trial.

b) Subjects with non-zero baseline concentrations > 5% of C_{max}. Such data should be excluded from bioequivalence calculation (see carry-over effects below).

The above can, for immediate release formulations, be the result of subject non-compliance and an insufficient wash-out period, respectively, and should as far as possible be avoided by mouth check of subjects after intake of study medication to ensure the subjects have swallowed the study medication and by designing the study with a sufficient wash-out period. The samples from subjects excluded from the statistical analysis should still be assayed and the results listed (see Presentation of data below).

As stated in Section 3.1.4, $AUC_{(0-t)}$ should cover at least 80% of $AUC_{(0-\infty)}$. Subjects should not be excluded from the statistical analysis if $AUC_{(0-t)}$ covers less than 80% of AUC (0 - ∞), but if the percentage is less than 80% in more than 20% of the observations then the validity of the study may need to be discussed. This does not apply if the sampling period is 72 h or more and $AUC_{(0-72h)}$ is used instead of $AUC_{(0-t)}$.

Parameters to be analysed and acceptance limits

In studies to determine bioequivalence after a single dose, the parameters to be analysed are $AUC_{(0-t)}$, or, when relevant, $AUC_{(0-72h)}$, and C_{max}. For these

parameters the 90% confidence interval for the ratio of the test and comparator products should be contained within the acceptance interval of 80.00-125.00%. To be inside the acceptance interval the lower bound should be ≥ 80.00% when rounded to two decimal places and the upper bound should be ≤ 125.00% when rounded to two decimal places.

For studies to determine bioequivalence of immediate release formulations at steady state, $AUC_{(0-\tau)}$ and $C_{max,ss}$ should be analysed using the same acceptance interval as stated above.

In the rare case where urinary data has been used, $Ae_{(0-t)}$ should be analysed using the same acceptance interval as stated above for $AUC_{(0-t)}$. R max should be analysed using the same acceptance interval as for C_{max}.

A statistical evaluation of t_{max} is not required. However, if rapid release is claimed to be clinically relevant and of importance for onset of action or is related to adverse events, there should be no apparent difference in median T_{max} and its variability between test and comparator product.

In specific cases of products with a narrow therapeutic range, the acceptance interval may need to be tightened (see Section 3.1.9). Moreover, for highly variable finished pharmaceutical products the acceptance interval for C_{max} may in certain cases be widened (see Section 3.1.10).

Statistical analysis

The assessment of bioequivalence is based upon 90% confidence intervals for the ratio of the population geometric means (test/comparator) for the parameters under consideration. This method is equivalent to two one-sided tests with the null hypothesis of bioequivalence at the 5% significance level.

The pharmacokinetic parameters under consideration should be analysed using ANOVA. The data should be transformed prior to analysis using a logarithmic transformation. A confidence interval for the difference between formulations on the log-transformed scale is obtained from the ANOVA model. This confidence interval is then back-transformed to obtain the desired confidence interval for the ratio on the original scale. A non-parametric analysis is not acceptable.

The precise model to be used for the analysis should be pre-specified in the

protocol. The statistical analysis should take into account sources of variation that can be reasonably assumed to have an effect on the response variable. The terms to be used in the ANOVA model are usually sequence, subject within sequence, period and formulation. Fixed effects, rather than random effects, should be used for all terms.

Carry-over effects

A test for carry-over is not considered relevant and no decisions regarding the analysis (e.g. analysis of the first period only) should be made on the basis of such a test. The potential for carry-over can be directly addressed by examination of the pre-treatment plasma concentrations in period 2 (and beyond if applicable).

If there are any subjects for whom the pre-dose concentration is greater than 5 percent of the C_{max} value for the subject in that period, the statistical analysis should be performed with the data from that subject for that period excluded. In a 2-period trial this will result in the subject being removed from the analysis. The trial will no longer be considered acceptable if these exclusions result in fewer than 12 subjects being evaluable. This approach does not apply to endogenous drugs.

Two-stage design

It is acceptable to use a two-stage approach when attempting to demonstrate bioequivalence. An initial group of subjects can be treated and their data analysed. If bioequivalence has not been demonstrated an additional group can be recruited and the results from both groups combined in a final analysis. If this approach is adopted appropriate steps must be taken to preserve the overall type I error of the experiment and the stopping criteria should be clearly defined prior to the study.

The analysis of the first stage data should be treated as an interim analysis and both analyses conducted at adjusted significance levels (with the confidence intervals accordingly using an adjusted coverage probability which will be higher than 90%). For example, using 94.12% confidence intervals for both the analysis of stage 1 and the combined data from stage 1 and stage 2 would be

acceptable, but there are many acceptable alternatives and the choice of how much alpha to spend at the interim analysis is at the company's discretion. The plan to use a two-stage approach must be pre-specified in the protocol along with the adjusted significance levels to be used for each of the analyses.

When analysing the combined data from the two stages, a term for stage should be included in the ANOVA model.

Presentation of data

All individual concentration data and pharmacokinetic parameters should be listed by formulation together with summary statistics such as geometric mean, median, arithmetic mean, standard deviation, coefficient of variation, minimum and maximum. Individual plasma concentration/time curves should be presented in linear/linear and log/linear scale. The method used to derive the pharmacokinetic parameters from the raw data should be specified. The number of points of the terminal log-linear phase used to estimate the terminal rate constant (which is needed for a reliable estimate of AUC∞) should be specified.

For the pharmacokinetic parameters that were subject to statistical analysis, the point estimate and 90% confidence interval for the ratio of the test and comparator products should be presented.

The ANOVA tables, including the appropriate statistical tests of all effects in the model, should be submitted.

The report should be sufficiently detailed to enable the pharmacokinetics and the statistical analysis to be repeated, e.g. data on actual time of blood sampling after dose, drug concentrations, the values of the pharmacokinetic parameters for each subject in each period and the randomization scheme should be provided.

Drop-out and withdrawal of subjects should be fully documented. If available, concentration data and pharmacokinetic parameters from such subjects should be presented in the individual listings, but should not be included in the summary statistics.

The bioanalytical method should be documented in a pre -study validation report. A bioanalytical report should be provided as well. The bioanalytical

report should include a brief description of the bioanalytical method used and the results for all calibration standards and quality control samples. A representative number of chromatograms or other raw data should be provided covering the whole concentration range for all standard and quality control samples as well as the specimens analysed. This should include all chromatograms from at least 20% of the subjects with QC samples and calibration standards of the runs including these subjects.

If for a particular formulation at a particular strength multiple studies have been performed some of which demonstrate bioequivalence and some of which do not, the body of evidence must be considered as a whole. Only relevant studies, as defined in Section 3.0, need be considered. The existence of a study which demonstrates bioequivalence does not mean that those which do not can be ignored. The applicant should thoroughly discuss the results and justify the claim that bioequivalence has been demonstrated. Alternatively, when relevant, a combined analysis of all studies can be provided in addition to the individual study analyses. It is not acceptable to pool together studies which fail to demonstrate bioequivalence in the absence of a study that does.

3.1.9 Narrow therapeutic index drugs

In specific cases of products with a narrow therapeutic index, the acceptance interval for AUC should be tightened to 90.00-111.11%. Where C_{max} is of particular importance for safety, efficacy or drug level monitoring the 90.00-111.11% acceptance interval should also be applied for this parameter. Examples of narrow therapeutic index drugs (NTIDs), refer to the table below:

Aprindine	Carbamazepine
Clindamycin	Clonazepam
Clonidine	Cyclosporine
Digitoxin	Digoxin
Disopyramide	Ethinyl Estradiol
Ethosuximide	Guanethidine
Isoprenaline	Lithium Carbonate
Methotrexate	Phenobarbital
Phenytoin	Prazosin
Primidone	Procainamide

Quinidine	Sulfonylurea compounds
Tacrolimus	Theophylline compounds
Valproic Acid	Warfarin
Zonisamide	Glybuzole

3.1.10 Highly variable drugs or finished pharmaceutical products

Highly variable finished pharmaceutical products (HVDP) are those whose intra-subject variability for a parameter is larger than 30%. If an applicant suspects that a finished pharmaceutical product can be considered as highly variable in its rate and/or extent of absorption, a replicate cross-over design study can be carried out.

Those HVDP for which a wider difference in C max is considered clinically irrelevant based on a sound clinical justification can be assessed with a widened acceptance range. If this is the case the acceptance criteria for Cmax can be widened to a maximum of 69.84 – 143.19%. For the acceptance interval to be widened the bioequivalence study must be of a replicate design where it has been demonstrated that the within -subject variability for Cmax of the comparator compound in the study is >30%. The applicant should justify that the calculated intra-subject variability is a reliable estimate and that it is not the result of outliers. The request for a widened interval must be prospectively specified in the protocol.

The extent of the widening is defined based upon the within-subject variability seen in the bioequivalence study using scaled-average-bioequivalence according to [U, L] = exp [±k·sWR], where U is the upper limit of the acceptance range, L is the lower limit of the acceptance range, k is the regulatory constant set to 0.760 and sWR is the within-subject standard deviation of the log-transformed values of Cmax of the comparator product. The table below gives examples of how different levels of variability lead to different acceptance limits using this methodology.

Within-subject CV (%)*	**Lower Limit**	**Upper Limit**

30	80	125
35	77.23	129.48
40	74.62	134.02
45	72.15	138.59
≥50	69.84	143.19

$$CV(\%) = 100\sqrt{e^{s^2_{WR}} - 1}$$

The geometric mean ratio (GMR) should lie within the conventional acceptance range 80.00-125.00%.

The possibility to widen the acceptance criteria based on high intra-subject variability does not apply to AUC where the acceptance range should remain at 80.00 – 125.00% regardless of variability.

It is acceptable to apply either a 3-period or a 4-period crossover scheme in the replicate design study.

3.2 In vitro dissolution tests

General aspects of in vitro dissolution experiments are briefly outlined in (annex X) including basic requirements on how to use the similarity factor (f2-test).

3.2.1 In vitro dissolution tests complementary to bioequivalence studies

The results of in vitro dissolution tests at three different buffers (normally pH 1.2, 4.5 and 6.8) and the media intended for finished pharmaceutical product release (QC media), obtained with the batches of test and comparator products that were used in the bioequivalence study should be reported. Particular dosage forms like ODT (oral dispersible tablets) may require investigations using different experimental conditions. The results should be reported as profiles of percent of labelled amount dissolved versus time displaying mean values and summary statistics.

Unless otherwise justified, the specifications for the in vitro dissolution to be used for quality control of the product should be derived from the dissolution

profile of the test product batch that was found to be bioequivalent to the comparator product (see Annex I).

In the event that the results of comparative in vitro dissolution of the biobatches do not reflect bioequivalence as demonstrated in vivo the latter prevails. However, possible reasons for the discrepancy should be addressed and justified.

3.2.2 In vitro dissolution tests in support of biowaiver of strengths

Appropriate in vitro dissolution should confirm the adequacy of waiving additional in vivo bioequivalence testing. Accordingly, dissolution should be investigated at different pH values as outlined in the previous sections (normally pH 1.2, 4.5 and 6.8) unless otherwise justified. Similarity of in vitro dissolution (see Annex X) should be demonstrated at all conditions within the applied product series, i.e. between additional strengths and the strength(s) (i.e. batch(es)) used for bioequivalence testing.

At pH values where sink conditions may not be achievable for all strengths in vitro dissolution may differ between different strengths. However, the comparison with the respective strength of the comparator medicinal product should then confirm that this finding is active pharmaceutical ingredient rather than formulation related. In addition, the applicant could show similar profiles at the same dose (e.g. as a possibility two tablets of 5 mg versus one tablet of 10 mg could be compared).

3.3 Study report

3.3.1 Bioequivalence study report

The report of a bioavailability or bioequivalence study should follow the template format as provided in the Comprehensive Bioequivalence Information Summary (CBIS), Annex XI) in order to submit the complete documentation of its conduct and evaluation complying with GCP-rules.

The report of the bioequivalence study should give the complete documentation of its protocol, conduct, and evaluation. It should be written in accordance with the ICH E3 guideline and be signed by the investigator.

Names and affiliations of the responsible investigator(s), the site of the study and the period of its execution should be stated. Audit's certificate(s), if available, should be included in the report.

The study report should include evidence that the choice of the comparator medicinal product is in accordance with PPB list of comparator products. This should include the comparator product name, strength, pharmaceutical form, batch number, manufacturer, expiry date and country of purchase.

The name and composition of the test product(s) used in the study should be provided. The batch size, batch number, manufacturing date and, if possible, the expiry date of the test product should be stated.

Certificates of analysis of comparator and test batches used in the study should be included in an Annex to the study report.

Concentrations and pharmacokinetic data and statistical analyses should be presented in the level of detail described above (Section 3.1.8 Presentation of data).

3.3.2 Other data to be included in an application

The applicant should submit a signed statement confirming that the test product has the same quantitative composition and is manufactured by the same process as the one submitted for authorization. A confirmation whether the test product is already scaled-up for production should be submitted. Comparative dissolution profiles (see Section 3.2) should be provided.

The validation report of the bioanalytical method should be included in Module 5 of the application.

Data sufficiently detailed to enable the pharmacokinetics and the statistical analysis to be repeated, e.g. data on actual times of blood sampling, drug concentrations, the values of the pharmacokinetic parameters for each subject in each period and the randomization scheme, should be available in a suitable electronic format (e.g. as comma separated and space delimited text files or Excel format) to be provided upon request.

3.4 Variation applications

If a product has been reformulated from the formulation initially approved or the manufacturing method has been modified in ways that may impact on the bioavailability, an in vivo bioequivalence study is required, unless otherwise justified. Any justification presented should be based upon general considerations, e.g. as per Annex IX.

In cases where the bioavailability of the product undergoing change has been investigated and an acceptable level A correlation between in vivo performance and in vitro dissolution has been established, the requirements for in vivo demonstration of bioequivalence can be waived if the dissolution profile in vitro of the new product is similar to that of the already approved medicinal product under the same test conditions as used to establish the correlation (see Annex XII).

For variations of products approved on full documentation on quality, safety and efficacy, the comparative medicinal product for use in bioequivalence and dissolution studies is usually authorized under the currently registered formulation, manufacturing process, packaging etc.

When variations to a generic product are made, the comparative medicinal product for the bioequivalence study should normally be a current batch of the reference medicinal product. If a valid reference medicinal product is not available on the market, comparison to the previous formulation (of the generic product) could be accepted, if justified. For variations that do not require a bioequivalence study, the advice and requirements stated in other published regulatory guidance should be followed.

3.5 Other Approaches to Assess Therapeutic Equivalence

3.5.1 Comparative pharmacodynamics studies

Studies in healthy volunteers or patients using pharmacodynamics measurements may be used for establishing equivalence between two pharmaceutical products. These studies may become necessary if quantitative analysis of the drug and/or metabolite(s) in plasma or urine cannot be made with sufficient accuracy and sensitivity. Furthermore,

pharmacodynamics studies in humans are required if measurements of drug concentrations cannot be used as surrogate end points for the demonstration of efficacy and safety of the particular pharmaceutical product e.g., for topical products without intended absorption of the drug into the systemic circulation.

3.5.2 Comparative clinical studies

If a clinical study is considered as being undertaken to prove equivalence, the same statistical principles apply as for the bioequivalence studies. The number of patients to be included in the study will depend on the variability of the target parameters and the acceptance range, and is usually much higher than the number of subjects in bioequivalence studies.

3.5.3 Special considerations for modified–release finished pharmaceutical products

For the purpose of these guidelines modified release products include:

i. Delayed release
ii. Sustained release
iii. Mixed immediate and sustained release
iv. Mixed delayed and sustained release
v. Mixed immediate and delayed release

Generally, these products should:

i. Acts as modified –release formulations and meet the label claim.
ii. Preclude the possibility of any dose dumping effects.
iii. There must be a significant difference between the performance of a modified release product and the conventional release product when used as a reference product.
iv. Provide a therapeutic performance comparable to the reference immediate – release formulation administered by the same route in multiple doses (of an equivalent daily amount) or to the reference modified – release formulation.
v. Produce consistent Pharmacokinetic performance between individual dosage units and

vi. Produce plasma levels which lie within the therapeutic range (where appropriate) for the proposed dosing intervals at steady state.

If all of the above conditions are not met but the applicant considers the formulation to be acceptable, justification to this effect should be provided.

a) Study Parameters

Bioavailability data should be obtained for all modified release finished pharmaceutical products although the type of studies required and the Pharmacokinetics parameters which should be evaluated may differ depending on the active ingredient involved. Factors to be considered include whether or not the formulation represents the first market entry of the active pharmaceutical ingredients, and the extent of accumulation of the drug after repeated dosing.

If formulation is the first market entry of the APIs, the products pharmacokinetic parameters should be determined. If the formulation is a second or subsequent market entry then the comparative bioavailability studies using an appropriate reference product should be performed.

b) Study design

Study design will be single dose or single and multiple dose based on the modified release products that are likely to accumulate or unlikely to accumulate both in fasted and non- fasting state. If the effects of food on the reference product is not known (or it is known that food affects its absorption), two separate two –way cross –over studies, one in the fasted state and the other in the fed state, may be carried out.

c) Requirement for modified release formulations unlikely to accumulate

This section outlines the requirements for modified release formulations which are used at a dose interval that is not likely to lead to accumulation in the body (AUC_{0-v} /$AUC_{0-\infty} \geq 0.8$)

When the modified release product is the first marketed entry type of dosage form, the reference product should normally be the innovator immediate – release formulation. The comparison should be between a single dose of the modified release formulation and doses of the immediate – release formulation which it is intended to replace. The latter must be administered according to the established dosing regimen.

When the release product is the second or subsequent entry on the market, comparison should be with the reference modified release product for which bioequivalence is claimed.

Studies should be performed with single dose administration in the fasting state as well as following an appropriate meal at a specified time.

The following pharmacokinetic parameters should be calculated from plasma (or relevant biological matrix) concentration of the drug and /or major metabolites(s) AUC_{0-t} AUC_{0-t} $AUC_{0-\infty}$, C_{max} (where the comparison is with an existing modified release product) and $K_{el.}$

The 90% confidence interval calculated using log transformed data for the ratios (Test vs Reference) of the geometric mean AUC (for both AUC_{0-t} and AUC_{0-t}) and C_{max} (Where the comparison is with an existing modified release product) should generally be within the range 80 to 125% both in the fasting state and following the administration of an appropriate meal at a specified time before taking the drug.

The Pharmacokinetic parameters should support the claimed dose delivery attributes of the modified release – dosage form.

d) Requirement for modified release formulations likely to accumulate

This section outlines the requirement for modified release formulations that are used at dose intervals that are likely to lead to accumulation (AUC /AUC c o.8).

When a modified release product is the first market entry of the modified release type, the reference formulation is normally the innovators immediate – release formulation. Both a single dose and steady state doses of the

modified release formulation should be compared with doses of the immediate - release formulation which it is intended to replace. The immediate – release product should be administered according to the conventional dosing regimen.

Studies should be performed with single dose administration in the fasting state as well as following an appropriate meal. In addition, studies are required at steady state. The following pharmacokinetic parameters should be calculated from single dose studies; $AUC_{0-t,}$ $AUC_{0-t,}$ $AUC_{0-\infty}$ C_{max} (where the comparison is with an existing modified release product) and K_{el}. The following parameters should be calculated from steady state studies; AUC_{0-t} C_{max} C_{min} C_{pd}, and degree of fluctuation.

When the modified release product is the second or subsequent modified release entry, single dose and steady state comparisons should normally be made with the reference modified release product for which bioequivalence is claimed.

90% confidence interval for the ration of geometric means (Test Reference drug) for $AUC_{o-t()}$,C_{max}, and C_{min} determined using log –transferred data should generally be within the range 80 to 125% when the formulation are compared at steady state.

The Pharmacokinetic parameters should support the claimed attributes of the modified – release dosage form.

The Pharmacokinetic data may reinforce or clarify interpretation of difference in the plasma concentration data.

Where these studies do not show bioequivalence, comparative efficacy and safety data may be required for the new product.

3.5.4 Pharmacodynamic studies;

Studies in healthy volunteers or patients using pharmacodynamics parameters may be used for establishing equivalence between two pharmaceutical products. These studies may become necessary if quantitative analysis of the drug and /or metabolites (s) in plasma or urine cannot be made with sufficient accuracy and sensitivity. Furthermore,

pharmacodynamic studies in humans are required if measurement of drug concentrations cannot be used as surrogate endpoints for the demonstration of efficacy and safety of the particular pharmaceutical product e.g for topical products without an intended absorption of the drug into the systemic circulation.

In case, only pharmacodynamic data is collected and provided, the applicant should outline what other methods were tried and why they were found unsuitable.

The following requirements should be recognized when planning, conducting and assessing the results from a pharmacodynamic study;

i. The response measured should be a pharmacological or therapeutically effects which is relevant to the claims of efficacy and /or safety of the drug.
ii. The methodology adopted for carrying out the study the study should be validated for precision, accuracy, reproducibility and specificity.
iii. Neither the test nor reference product should produce a maximal response in the course of the study, since it may be impossible to distinguish difference between formulations given in doses that produce such maximal responses. Investigation of dose – response relationship may become necessary.
iv. The response should be measured quantitatively under double – blind conditions and be recorded in an instrument – produced or instrument recorded fashion on a repetitive basis to provide a record of pharmacodynamic events which are suitable for plasma concentrations. If such measurement is not possible recording on visual – analog scales may be used. In instances where data are limited to quantitative (categorized) measurement, appropriate special statistical analysis will be required.
v. Non – responders should be excluded from the study by prior screening. The criteria by which responder `-are versus non – responders are identified must be stated in the protocol.

vi. Where an important placebo effect occur comparison between products can only be made by a priori consideration of the placebo effect in the study design. This may be achieved by adding a third period/phase with placebo treatment, in the design of the study.

vii. A crossover or parallel study design should be used, appropriate.

viii. When pharmacodynamic studies are to be carried out on patients, the underlying pathology and natural history of the condition should be considered in the design.

ix. There should be knowledge of the reproducibility of the base – line conditions.

x. Statistical considerations for the assessments of the outcomes are in principle, the same as in Pharmacokinetic studies.

xi. A correction for the potential non – linearity of the relationship between dose and area under the effect – time curve should be made on the basis of the outcome of the dose ranging study.

The conventional acceptance range as applicable to Pharmacokinetic studies and bioequivalence is not appropriate (too large) in most cases. This range should therefore be defined in the protocol on a case – to – case basis.

3.5.5 Comparative clinical studies

The plasma concentration time – profile data may not be suitable to assess equivalence between two formulations. Whereas in some of the cases pharmacodynamic studies can be an appropriate to for establishing equivalence, in other instances this type of study cannot be performed because of lack of meaningful pharmacodynamic parameters which can be measured and comparative clinical study has be performed in order to demonstrate equivalence between two formulations. Comparative clinical studies may also be required to be carried out for certain orally administered finished pharmaceutical products when pharmacokinetic and pharmacodynamic studies are no feasible. However, in such cases the applicant should outline what other methods were why they were found unsuitable.

If a clinical study is considered as being undertaken to prove equivalence, the appropriate statistical principles should be applied to demonstrate bioequivalence. The number of patients to be included in the study will depend on the variability of the target parameter and the acceptance range, and is usually much higher than the number of subjects in bioequivalence studies.

The following items are important and need to be defined in the protocol advance:

a) The target parameters which usually represent relevant clinical end – points from which the intensity and the onset, if applicable and relevant, of the response are to be derived.
b) The size of the acceptance range has to be defined case taking into consideration the specific clinical conditions. These include, among others, the natural course of the disease, the efficacy of available treatment and the chosen target parameter. In contrast to bioequivalence studies (where a conventional acceptance range is applied) the size of the acceptance in clinical trials cannot be based on a general consensus on all the therapeutic clinical classes and indications.
c) The presently used statistical method is the confidence interval approach. The main concern is to rule out t Hence, a one – sided confidence interval (For efficacy and/or safety) may be appropriate. The confidence intervals can be derived from either parametric or nonparametric methods.
d) Where appropriate, a placebo leg should be included in the design.
e) In some cases, it is relevant to include safety end-points in the final comparative assessments.

ANNEXES

Annex IX: Bioequivalence Trial Information (BTIF) Form

General Instructions:

Please review all the instructions thoroughly and carefully prior to completing the Bioequivalence Trial Information Form (BTIF).

Provide as much detailed, accurate and final information as possible. Note that the greyed areas are NOT to be filled in by the applicant but are for PPB use ONLY!

Please state the exact location (Annex number) of appended documents in the relevant sections of the BTIF. For example, in section 3.4.3.1 under point b), indicate in which Annex (number) the Certificate of Analysis can be found. This procedure must be followed throughout the entire document where location of annexed documents is requested. Before submitting the completed BTIF, kindly check that you have provided all requested information and enclosed all requested documents.

Should you have any questions regarding this Form, please contact Pharmacy and Poisons Board (PPB) through Deputy Director, Product Evaluation and Registration Department.

A properly filled out and signed original copy of the BTIF with all its annexes (including a copy on CD-ROM) must be submitted to the PPB together with the bioequivalence part of the dossier to the address below.

Chief Executive Officer,
Pharmacy & Poisons Board
P.O. Box 27663 – 00506, Nairobi.
Lenana Road Opp. DOD

Assessment Report for Generic Finished Pharmaceutical Products (FPPs) not registered in ICH regions or related countries

BIOEQUIVALENCE PART OF A NEW DOSSIER		
Reference of the session		
Application Number		
Date of submission of the dossier		
Date of evaluation		
Type of product		
Type of dossier	**EFFICACY**	
Type of submission	**NEW**	
First assessor	Name	Signature
Second assessor/Plenary session	Name	Signature
Quality assessor (e.g., when dissolution profiles are submitted for comparison of the compositions of clinical, stability and validation batches, or a biowaiver for additional strengths is requested.)	Name	Signature
Reference Number		
Number of binders		
SPC , PIL submitted	(state location in submission)	
SPC, PIL, Package Labelling acceptable	Yes:_____// No:_____	
Proprietary Product Name (if relevant)	*..	
International Non-proprietary Name (INN) of the Active Pharmaceutical Ingredient (API), strength, pharmaceutical form.	*..	
Conclusion of the assessment	**ACCEPTED (no outstanding issues)** **ADDITIONAL DATA REQUESTED** **REJECTED** ***(Please delete the wrong entries)***	
Name and complete address of the supplier (Applicant of the dossier)	*..	

Name and address of the Contract Research Organization(s) where the clinical studies proving efficacy and safety of the product were conducted. *(Add as much rows as necessary)*	*..
This product assessment report should be written in clear unambiguous language referring to deficiencies or lack of data submitted, as communication with the manufacturer may result from the assessment. The report should be completed by at least two evaluators or one evaluator and plenary for quality assurance purposes. The assessment report should be typed with "Bookman Old Style 12" fonts. The format of tables must not be changed.	

BIOEQUIVALENCE TRIAL INFORMATION:

1. **SUMMARY BIOAVAILABILITY/BIOEQUIVALENCE STUDIES PERFORMED**

(Provide a brief description of each comparative bioavailability study included in the submission)

2. **TABULATION OF THE COMPOSITION OF THE FORMULATION(S) PROPOSED FOR MARKETING AND THOSE USED FOR BIOEQUIVALENCE STUDIES**

(State the location of the master formulae in the quality part of the submission)
(Tabulate the composition of the bio batch using the table below. For solid oral dosage forms the table should contain only the ingredients in tablet core /contents of a capsule. A copy of the table should be filled in for the film coating / hard capsule, if any.
***Important**: If the* formulation proposed for marketing and those used for bioequivalence studies are not identical, copies of this table should be filled in for each formulation with clear identification in which bioequivalence study the respective formulation was used.)

2.1 Has comparative bioavailability data been submitted for all strengths?

(If comparative bioavailability data has not been submitted for all strengths, provide a scientific justification for not submitting such data; append copies of all references cited in the justification. Justification should include – but is not limited to – argumentation related to dose-proportional composition, dose-

linearity of pharmacokinetics (Cmax and AUC,), discriminatory (with regard to bioavailability differences) power of dissolution tests employed)

Sections 3.0 – 11.0 below should be copied and completed separately for each bioequivalence study performed.

Batch number					
Batch size (number of unit doses)					
Comments, if any					
Comparison of unit dose compositions and of clinical FPP batches *(Duplicate this table for each strength, if compositions are different)*					
Ingredients (and quality standard)	*Function*	*Unit dose (mg)*	*Unit dose (%)*	*Biobatch (kg)*	*Biobatch (%)*
Total					
Equivalence of the compositions or justified differences					

Maximum intended commercial batch size	

Bioequivalence batches should be at least of pilot scale (10% of production scale or 100,000 capsules/tablets whichever is the greater) and manufacturing method should be the same as for production scale.

3. CLINICAL STUDY REPORT

a) Study number:
b) Study title:
c) Study Design
d) Location of study protocol:
e) Start and stop dates for each phase of the clinical study:
f) Dates of product administration:

1.1 ETHICS

a) State the name of review committee, date of approval of protocol and consent form and the location of approval letter in the submission
b) State location of a reference copy of the informed consent form

1.2 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

a) Name of principal investigator(s) (State location of c.v. in the submission)
b) Clinical Facility (Name and full mailing address)
c) Clinical Laboratories (Name and full mailing address)
d) Analytical Laboratories (Name and full mailing address)
e) Company performing pharmacokinetic/statistical analysis (Name and full mailing address)

1.3 STUDY OBJECTIVES

Briefly state the study objectives.

1.4 INVESTIGATIONAL PLAN

1.4.1 Overall study design and plan — description

(Describe the type of study design employed in 1-2 sentences)

1.4.2 Selection of study population

1.4.2.1 Inclusion Criteria

(List the inclusion criteria applied to subjects)

1.4.2.2 Exclusion Criteria

(List the exclusion criteria applied to subjects)

1.4.2.3 Health Verification

(State location of the individual data included in the submission)

a. List criteria used and all tests performed in order to judge health status

b. Indicate when tests were performed

c. Study site normal values
(State location in submission of study site normal values for blood clinical chemistry, haematology, and urinalysis clinical screen)

d. Report any results that were outside of study site normal values
(State location in submission of the summary of anomalous values)

1.4.2.4 Removal of Trial subjects from Trial or Assessment

a) Number of subjects enrolled in the study
(All subjects including alternates, withdrawals, and dropouts)

b) Alternates
(Please note: Generally, all subjects enrolled in the study should be included in the data set i.e., alternate subjects are strongly discouraged. However, in cases where there are alternate subjects, describe the procedure of including/excluding the alternates and whether alternates have been included in the study)

c) Withdrawals/dropouts

(Identify each withdrawal/dropout by subject and provide the reason for withdrawal/dropout and at what point in the study the withdrawal/dropout occurred)

1.4.3 Products Administered

1.4.3.1 Test Product

a) Batch number, size, date of manufacture and expiry date for the test product

b) Potency (measured content) of test product as a percentage of label claim as per validated assay method

(This information should be cross-referenced to the location of the certificate of analysis in the submission)

1.4.3.2 Comparator (Reference) Product

(Append to this template a copy of product labelling (snap shot of the box, on which the name of the product, name and address of the manufacturer, batch number, and expiry date are clearly visible on the labelling)

a) Name and manufacturer of the comparator product and market where the comparator product was purchased
b) Batch number and expiry date for the comparator product
c) Purchase, shipment, storage of the comparator product

(Indicate from which company/pharmaceutical distributor the comparator product has been obtained. Clearly indicate in chronological order the steps and dates of shipment/transport from company of purchase to the study site. In addition, the storage conditions should be given. This information should be cross-referenced to location in submission of documents (e.g. receipts) proving conditions)

Potency (measured content) of the comparator product as a percentage of label claim, as measured by the same laboratory and under the same conditions as the test product

(This information should be cross-referenced to the location of the certificate of analysis in the submission)

Justification of choice of comparator product

(Provide short summary here and cross-reference to location of comprehensive justification in study protocol)

1.4.4 Selection of doses in the study

a) State dose administered

(Indicate the number of dosage units comprising a single dose, e.g., 400 mg as 1 x 400 mg or 2 x 200 mg tablets)

1.4.5 Selection and Timing of Dose for Each Subject

a) State volume and type of fluid consumed with dose

b) Interval between doses *(i.e., length of washout)*

c) Protocol for the administration of food and fluid

d) Restrictions on posture and physical activity during the study

1.4.6 Blinding

1.4.6.1 Identify which of the following were blinded. If any of the groups were not blinded, provide a justification for not doing so.

a) study monitors: Yes ☐ / No ☐ If no, justify:

b) subjects: Yes ☐ / No ☐ If no, justify:

c) analysts: Yes / No If no, justify:

1.4.6.2 Identify who held the study code and when the code was broken

1.4.7 Drug Concentration Measurements

1.4.7.1 Biological fluid(s) sampled

1.4.7.2 Sampling protocol

a) Number of samples collected per subject

b) Volume of fluid collected per sample

c) Total volume of fluid collected per subject per phase of the study

d) List the study sampling times

e) Identify any deviations from the sampling protocol

(State location of summary in the submission)

(Describe and explain reasons for deviations from sampling protocol. Comment on impact on study. Indicate whether the deviations were accounted for in the pharmacokinetic analysis)

1.4.7.3 Sample Handling

a) Describe the method of sample collection

b) Describe sample handling and storage procedures

Comments from review of Section 2 – PPB use only

4. TRIAL SUBJECTS

4.1 Demographic and other baseline characteristics

a) Identify study population (i.e., normal, healthy adult volunteers or patients)

b) Summary of ethnic origin and gender of subjects

c) Identify subjects noted to have special characteristics and state notable characteristics *(e.g. fast acetylators of debrisoquine)*

d) Range and mean age ± SD of subjects

e) Range and mean height and weight ± SD of subjects

f) Identify subjects whose ratio is not within 15% of the values given on a standard height/weight table

4.2 Subjects who smoke

a) Number of smokers included in the study

b) Indicate how many cigarettes smoked per day per subject

c) Comment on the impact on study

Comments from review of Section 3 – PPB use only

5. PROTOCOL DEVIATIONS

5.1 Protocol deviations during the clinical study

(Describe any such deviations and discuss their implications with respect to bioequivalence)

Comments from review of Section 4 – PPB use only

6. SAFETY EVALUATION

6.1 Identify adverse events observed

(List any adverse events by subject number. State whether a reaction occurred following administration of the test or reference product, identify any causal relationships, and note any treatments required. State location of this summary in the submission.)
(Discuss the implications of the observed adverse events with respect to bioequivalence.)

Comments from review of Section 5 – PPB use only

7. EFFICACY EVALUATION

Efficacy results and tabulations of individual trial subjects' data

7.1 Presentation of data

a) State location in submission of tables of mean and individual subject concentrations
b) State location in submission of (mean and individual) linear and semi-logarithmic subject drug concentration vs. time plots

7.2 Pharmacokinetic (PK) parameters

a) State how the pharmacokinetic parameters where calculated/obtained for $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, C_{max}, tmax, the elimination rate constant, and $t_{½}$ (indicate location of description in protocol)

b) State whether actual sampling time points were used for estimation of the pharmacokinetic parameters

c) Complete the table below

		Test			Reference	
Parameter	Arithmetic mean	Standard deviation	Interindividual coefficient of variation (%)Number range CHAPTER	Arithmetic mean	Standard deviation	Interindividual coefficient of variation (%)Number range CHAPTER
AUC0-t (units)						
AUC0-inf (units)						
Cmax (units)						
tmax (units)						
t½ (units)						

d) Ratio of $AUC_{0\text{-}t}$ to $AUC_{0\text{-}inf}$

(State mean ratio for both test and reference, state location in submission where individual ratios can be found)

7.3 Statistical analysis

(State the method of calculation of the 90% confidence intervals for the ratio of test formulation over the reference formulation and indicate how treatment, period, sequence and subjects within sequence were included as factors in the ANOVA. Provide the following results from the ANOVA (parametric) on the logarithmically transformed AUC0-t and CMAX and other relevant parameters. State software used for computing ANOVA.)

a) Geometric means, results from ANOVA, Degrees of Freedom (DF) and derived CV (intra-subject)

b) Comparison of the results

(Compare the results, including mean values, inter- and intra-individual variability, of this study with published results (literature, product information of reference product (innovator), WHOPARs), and copies of the references used should be appended to this document)

7.4 Discussion of results

(State location of the discussion of the results in the submission)

Comments from review of Section 6 – PPB use only

8. ANALYTICAL VALIDATION REPORT

8.1 Analytical technique

8.1.1 Validation protocol

(State the location of the validation protocol)

8.1.2 Identify analyte(s) monitored

8.1.3 Comment on source and validity of reference standard

8.1.4 Identify internal standard

8.1.5 Identify method of extraction

8.1.6 Identify analytical technique or method of separation employed

8.1.7 Identify method of detection

8.1.8 Identify anticoagulant used (if applicable)

8.1.9 If based on a published procedure, state reference citation

8.1.10 Identify any deviations from protocol

8.1.11 Dates of subject sample analysis

8.1.12 Longest period of subject sample storage

8.1.13 State whether all samples for a given subject were analysed together in a single analysis run

8.2 Selectivity

(Address the methods to verify selectivity against endogenous/exogenous compounds & results)

8.3 Sensitivity

(Address the methods to verify sensitivity & results)

8.4 Carry-over

(Summarize the method to verify carry-over & results)

8.5 Standard curves

(State location in submission of tabulated raw data and back calculated data with descriptive statistics)

a) List number and concentration of calibration standards used

b) Describe the regression model used including any weighting

c) List the back-calculated concentrations of the calibration standards of the validation runs *(highlight the values outside of the acceptance range, e.g., 15%, except 20% for LLOQ)*

8.6 Quality control samples

a) Identify the concentrations of the QC samples and the storage conditions employed prior to their analysis

8.7 Precision and accuracy during validation

a) Summarize inter-day/inter-run accuracy and precision of the calibration standards during assay validation

b) Summarize inter-day/inter-run accuracy and precision of the calibration standards during assay re-validation

(If applicable)

c) Summarize inter-day/inter-run and intra-day/intra-run accuracy and precision of the QC samples during assay validation

d) Summarize inter-day/inter-run and intra-day/intra-run accuracy and precision of the QC samples during assay re-validation *(If applicable)*

8.8 Dilution integrity

(Summarize the method to verify dilution integrity & results)

8.9 Matrix effect (in case of MS detection)

(Summarize methods to verify the matrix effect & results)

8.10 Stability

(For each section provide the location of the raw data, a description of the methodology employed and a summary of the data.)

a) Summarize data on long-term storage stability

b) Summarize data on freeze-thaw stability

c) Summarize data on bench top stability

d) Summarize data on auto-sampler storage stability

e) Summarize data from any other stability studies conducted

(e.g. long-term stock solution and working solution stability, short-term stock solution and working solution stability, dry-extract stability, wet-extract stability, stability in blood before sample processing)

8.11 Re-injection reproducibility

(Summarize the method to verify re-injection reproducibility & results)

Comments from review of Section 7 – PPB use only

9. BIOANALYTICAL STUDY REPORT

(State the location of the bioanalytical report for the analysis of the study subject samples)

9.1 Analytical technique

(Confirm whether the method is the same as the validated method and whether the same equipment was employed. Identify any differences between the validated method described above in Section 7 and the method employed for subject sample analyses)

9.1.1 Analytical protocol

(State the location of the analytical protocol)

9.1.2 Identify any deviations from protocol

9.1.3 Dates of subject sample analysis

9.1.4 Longest period of subject sample storage

(Identify the time elapsed between the first day of sample collection and the last day of subject sample analysis)

9.1.5 State whether all samples for a given subject were analysed together in a single analysis run

9.2 Standard curves

(State location in submission of tabulated raw data and back calculated data with descriptive statistics)

a) List number and concentration of calibration standards used

b) State number of curves run during the study *(valid and failed runs, including reasons of failure).*

c) Summarize descriptive data including slope, intercept, correlation coefficients

d) List the back-calculated concentrations of the calibration standards of the study runs *(highlight the values outside of the acceptance range, e.g., 15%, except 20% for LLOQ)*

9.3 Quality control samples

a) Identify the concentrations of the QC samples, their date of preparation and the storage conditions employed prior to their analysis

b) State the number of QC samples in each analytical run per concentration

c) List the back-calculated concentrations of the QC samples of the study runs *(highlight the values outside of the acceptance range, e.g., 15%)*

d) Discuss whether the concentrations of the QC sample concentrations are similar to the concentrations observed in the study samples

e) State the percentage of QC samples per run with respect to the total number samples assayed in each run

9.4 Precision and accuracy

a) Summarize inter-day precision of back-calculated standards and inter-day and intra-day precision and accuracy of QC samples analysed during subject sample analysis

9.5 Repeat analysis (re-analysis, re-injection and re-integration)

a) List re-analysed samples by sample identification and include the following information for each re-analysis: initial value; reason for re-analysis; re-analysed value(s); accepted value; and reason for acceptance

b) Report the number of re-analysis as a percentage of the total number samples assayed

c) List re-injected samples by sample identification and include the following information for each re-injection: initial value; reason for re-injection; re-injected value; accepted value; and reason for acceptance

d) Report the number of re-injections as a percentage of the total number samples assayed

e) List re-integrated chromatograms by sample identification and include the following information for each re-integration: initial value; reason for re-integration; re-integrated value(s); accepted value; and reason for acceptance

f) Report the number of re-integrated chromatograms as a percentage of the total number of samples assayed

9.6 Incurred sample reanalysis

(State location in the submission and summarize the results of incurred sample reanalysis, including the number of subject samples included in ISR and the total number of samples analysed in the study)

9.7 Chromatograms

(State the location in the submission where the sample chromatograms can be found. The chromatograms should be obtained from a minimum of two analytical batches and include at least 20% of the subjects, up to a maximum of five. A complete set includes standards, QC samples, pre-dose and post-dose subject samples for both phases. Each chromatogram should be clearly labelled with respect to the following: date of analysis; subject ID number; study period; sampling time; analyte; standard or QC, with concentration; analyte and internal standard peaks; peak heights and/or areas)

Comments from review of Section 9 – PPB use only

10. QUALITY ASSURANCE

10.1 Internal quality assurance methods

(State locations in the submission where internal quality assurance methods and results are described for each of study sites (see 3.2 b-d.)

10.2 Monitoring, auditing, inspections

(Provide a list of all monitoring and auditing reports of the study, and of recent inspections of study sites by regulatory agencies. State locations in the submission of the respective reports for each study site (see 3.2 b-d.)

Comments from review of Section 10 – PPB use only

CONCLUSIONS AND RECOMMENDATIONS – PPB use only

Annex X: Dissolution testing and similarity of dissolution profiles

General aspects of dissolution testing as related to bioavailability

During the development of a medicinal product a dissolution test is used as a tool to identify formulation factors that are influencing and may have a crucial effect on the bioavailability of the drug. As soon as the composition and the manufacturing process are defined a dissolution test is used in the quality control of scale-up and of production batches to ensure both batch-to-batch consistency and that the dissolution profiles remain similar to those of pivotal clinical trial batches. Furthermore, in certain instances a dissolution test can be used to waive a bioequivalence study. Therefore, dissolution studies can serve several purposes: -

a) Testing on product quality: -

- To get information on the test batches used in bioavailability/bioequivalence studies and pivotal clinical studies to support specifications for quality control.
- To be used as a tool in quality control to demonstrate consistency in manufacture.
- To get information on the comparator product used in bioavailability/bioequivalence studies and pivotal clinical studies.

b) Bioequivalence surrogate inference

- To demonstrate in certain cases similarity between different formulations of an active substance and the reference medicinal product (biowaivers e.g., variations, formulation changes during development and generic medicinal products; see Section 3.2 and Biowaiver)
- To investigate batch to batch consistency of the products (test and comparator) to be used as basis for the selection of appropriate batches for the in vivo study.

Test methods should be developed product related based on general and/or specific pharmacopoeial requirements. In case those requirements are shown

to be unsatisfactory and/or do not reflect the in vivo dissolution (i.e.) alternative methods can be considered when justified that these are discriminatory and able to differentiate between batches with acceptable and non-acceptable performance of the product in vivo. Current state-of-the -art information including the interplay of characteristics derived from the BCS classification and the dosage form must always be considered.

Sampling time points should be sufficient to obtain meaningful dissolution profiles, and at least every 15 minutes. More frequent sampling during the period of greatest change in the dissolution profile is recommended. For rapidly dissolving products, where complete dissolution is within 30 minutes, generation of an adequate profile by sampling at 5- or 10-minute intervals may be necessary.

If an active substance is considered highly soluble, it is reasonable to expect that it will not cause any bioavailability problems if, in addition, the dosage system is rapidly dissolved in the physiological pH-range and the excipients are known not to affect bioavailability. In contrast, if an active substance is considered to have a limited or low solubility, the rate limiting step for absorption may be dosage form dissolution. This is also the case when excipients are controlling the release and subsequent dissolution of the active substance. In those cases, a variety of test conditions is recommended and adequate sampling should be performed.

Similarity of dissolution profiles

Dissolution profile similarity testing and any conclusions drawn from the results (e.g. justification for a biowaiver) can be considered valid only if the dissolution profile has been satisfactorily characterised using a sufficient number of time points.

For immediate release formulations, further to the guidance above, comparison at 15 min is essential to know if complete dissolution is reached before gastric emptying.

Where more than 85% of the drug is dissolved within 15 minutes, dissolution profiles may be accepted as similar without further mathematical evaluation.

In case more than 85% is not dissolved at 15 minutes but within 30 minutes, at least three time points are required: the first time point before 15 minutes, the second one at 15 minutes and the third time point when the release is close to 85%.

For modified release products, the advice given in the relevant guidance should be followed.

Dissolution similarity may be determined using the *f*2 statistic as follows:

$$f_2 = 50 \cdot \log\left[\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{t=n}\left[\overline{R}(t) - \overline{T}(t)\right]^2}{n}}}\right]$$

In this equation *f*2 is the similarity factor, n is the number of time points, R(t) is the mean percent reference drug dissolved at time t after initiation of the study; T(t) is the mean percent test drug dissolved at time t after initiation of the study. For both the reference and test formulations, percent dissolution should be determined.

The evaluation of the similarity factor is based on the following conditions:

- A minimum of three time points (zero excluded)
- The time points should be the same for the two formulations
- Twelve individual values for every time point for each formulation
- Not more than one mean value of > 85% dissolved for any of the formulations.

- The relative standard deviation or coefficient of variation of any product should be less than 20% for the first point and less than 10% from second to last time point.

An f2 value between 50 and 100 suggests that the two dissolution profiles are similar.

When the $f2$ statistic is not suitable, then the similarity may be compared using model-dependent or model-independent methods e.g. by statistical multivariate comparison of the parameters of the Weibull function or the percentage dissolved at different time points.

Alternative methods to the $f2$ statistic to demonstrate dissolution similarity are considered acceptable, if statistically valid and satisfactorily justified.

The similarity acceptance limits should be pre-defined and justified and not be greater than a 10% difference. In addition, the dissolution variability of the test and reference product data should also be similar; however, a lower variability of the test product may be acceptable.

Evidence that the statistical software has been validated should also be provided.

A clear description and explanation of the steps taken in the application of the procedure should be provided, with appropriate summary tables.

Annex XI: Bioequivalence study requirements for different dosage forms

Although this guideline concerns immediate release formulations, Annex XI provides some general guidance on the bioequivalence data requirements for other types of formulations and for specific types of immediate release formulations.

When the test product contains a different salt, ester, ether, isomer, mixture of isomers, complex or derivative of an active substance than the comparator medicinal product, bioequivalence should be demonstrated in in vivo bioequivalence studies. However, when the active substance in both test and comparator products is identical (or contain salts with similar properties), in vivo bioequivalence studies may in some situations not be required as described below and in **Annex XII**.

Oral immediate release dosage forms with systemic action

For dosage forms such as tablets, capsules and oral suspensions, bioequivalence studies are required unless a biowaiver is applicable (see **Annex XII**). For oral dispersible tablets and oral solutions specific recommendations apply, as detailed below.

Oral dispersible tablets

An oral dispersible tablet (ODT) is formulated to quickly disperse in the mouth. Placement in the mouth and time of contact may be critical in cases where the active substance also is dissolved in the mouth and can be absorbed directly via the buccal mucosa. Depending on the formulation, swallowing of the e.g. coated substance and subsequent absorption from the gastrointestinal tract also will occur. If it can be demonstrated that the active substance is not absorbed in the oral cavity, but rather must be swallowed and absorbed through the gastrointestinal tract, then the product might be considered for a BCS based biowaiver (see **Annex XII**). If this cannot be demonstrated, bioequivalence must be evaluated in human studies.

If the ODT test product is an extension to another oral formulation, a 3-period study is recommended in order to evaluate administration of the orodispersible tablet both with and without concomitant fluid intake.

However, if bioequivalence between ODT taken without water and comparator formulation with water is demonstrated in a 2-period study, bioequivalence of ODT taken with water can be assumed.

If the ODT is a generic to an approved ODT comparator medicinal product, the following recommendations regarding study design apply: -

- if the comparator medicinal product can be taken with or without water, bioequivalence should be demonstrated without water as this condition best resembles the intended use of the formulation. This is especially important if the substance may be dissolved and partly absorbed in the oral cavity. If bioequivalence is demonstrated when taken without water, bioequivalence when taken with water can be assumed.
- if the comparator medicinal product is taken only in one way (e.g. only with water), bioequivalence should be shown in this condition (in a conventional two-way crossover design).
- if the comparator medicinal product is taken only in one way (e.g. only with water), and the test product is intended for additional ways of administration (e.g. without water), the conventional and the new method should be compared with the comparator in the conventional way of administration (3 treatment, 3 period, 6 sequence design).

In studies evaluating ODTs without water, it is recommended to wet the mouth by swallowing 20 ml of water directly before applying the ODT on the tongue. It is recommended not to allow fluid intake earlier than 1 hour after administration.

Other oral formulations such as orodispersible films, buccal tablets or films, sublingual tablets and chewable tablets may be handled in a similar way as for ODTs. Bioequivalence studies should be conducted according to the recommended use of the product.

Annex XII: BCS-Based Biowaiver

I. Introduction

The BCS (Biopharmaceutics Classification System)-based biowaiver approach is meant to reduce *in vivo* bioequivalence studies, *i.e.*, it may represent a surrogate for *in vivo* bioequivalence. *In vivo* bioequivalence studies may be exempted if an assumption of equivalence in *in vivo* performance can be justified by satisfactory *in vitro* data.

Applying for a BCS-based biowaiver is restricted to highly soluble active pharmaceutical ingredients with known human absorption and considered not to have a narrow therapeutic index (see Section 3.1.9). The concept is applicable to immediate release, solid pharmaceutical products for oral administration and systemic action having the same pharmaceutical form. However, it is not applicable for sublingual, buccal, and modified release formulations. For oral dispersible formulations the BCS-based biowaiver approach may only be applicable when absorption in the oral cavity can be excluded.

BCS-based biowaivers are intended to address the question of bioequivalence between specific test and reference/comparator products. The principles may be used to establish bioequivalence in applications for generic medicinal products, extensions of innovator products, variations that require bioequivalence testing, and between early clinical trial products and to-be-marketed products.

In situations where multiples strength formulations have been submitted for BCS based biowaiver, comparative dissolution should be provided for all the strength.

II. Summary Requirements

BCS-based biowaiver are applicable for an immediate release finished pharmaceutical product if: -

- the active pharmaceutical ingredient has been proven to exhibit high solubility and complete absorption (BCS class I; for details see Section III) and

- either very rapid (> 85 % within 15 min) or similarly rapid (85 % within 30 min) *in vitro* dissolution characteristics of the test and reference product has been demonstrated considering specific requirements (see Section IV.1) and
- excipients that might affect bioavailability are qualitatively and quantitatively the same. In general, the use of the same excipients in similar amounts is preferred (see Section IV.2).

BCS-based biowaiver are also applicable for an immediate release finished pharmaceutical product if:-

- the active pharmaceutical ingredient has been proven to exhibit high solubility and limited absorption (BCS class III; for details see Section III) and
- very rapid (> 85 % within 15 min) *in vitro* dissolution of the test and reference product has been demonstrated considering specific requirements (see Section IV.1) and
- excipients that might affect bioavailability are qualitatively and quantitatively the same and
- other excipients are qualitatively the same and quantitatively very similar (see Section IV.2).

Generally, the risks of an inappropriate biowaiver decision should be more critically reviewed (e.g. site-specific absorption, risk for transport protein interactions at the absorption site, excipient composition and therapeutic risks) for products containing BCS class III than for BCS class I active pharmaceutical ingredient.

III. Active Pharmaceutical Ingredient

Generally, sound peer-reviewed literature may be acceptable for known compounds to describe the active pharmaceutical ingredient characteristics of importance for the biowaiver concept.

Biowaiver may be applicable when the active substance(s) in test and reference products are identical.

Biowaiver may also be applicable if test and reference contain different salts provided that both belong to BCS-class I (high solubility and complete absorption; see Sections III.1 and III.2). Biowaiver is not applicable when the test product contains a different ester, ether, isomer, mixture of isomers, complex or derivative of an active substance from that of the comparator product, since these differences may lead to different bioavailabilities not deducible by means of experiments used in the BCS-based biowaiver concept.

The active pharmaceutical ingredient should not belong to the group of 'narrow therapeutic index' drugs (see Section 4.1.9 on narrow therapeutic index drugs).

III.1 Solubility

The pH-solubility profile of the active pharmaceutical ingredient should be determined and discussed. An API is considered highly soluble when the highest single therapeutic dose as determined by the relevant regulatory authority, typically defined by the labeling for the innovator product, is completely dissolved in 250 ml of buffers within the range of pH 1 – 6.8 at 37±1 °C. This demonstration requires the investigation in at least three buffers within this range (preferably at pH 1.2, 4.5 and 6.8) and in addition at the pKa, if it is within the specified pH range. Replicate determinations at each pH condition may be necessary to achieve an unequivocal solubility classification (e.g. shake-flask method or other justified method). Solution pH should be verified prior and after addition of the active pharmaceutical ingredient to a buffer.

III.2 Absorption

The demonstration of complete absorption in humans is preferred for BCS-based biowaiver applications. For this purpose, complete absorption is considered to be established where measured extent of absorption is ≥ 85 %. Complete absorption is generally related to high permeability.

Complete drug absorption should be justified based on reliable investigations in human. Data from either: -

absolute bioavailability or

mass-balance

studies could be used to support this claim.

When data from mass balance studies are used to support complete absorption, it must be ensured that the metabolites taken into account in determination of fraction absorbed are formed after absorption. Hence, when referring to total radioactivity excreted in urine, it should be ensured that there is no degradation or metabolism of the unchanged active pharmaceutical ingredient in the gastric or intestinal fluid. Phase 1 oxidative and Phase 2 conjugative metabolism can only occur after absorption (i.e. cannot occur in the gastric or intestinal fluid). Hence, data from mass balance studies support complete absorption if the sum of urinary recovery of parent compound and urinary and faecal recovery of Phase 1 oxidative and Phase 2 conjugative drug metabolites account for ≥ 85 % of the dose.

In addition, highly soluble active pharmaceutical ingredients with incomplete absorption, i.e. BCS-class III compounds, could be eligible for a biowaiver provided certain prerequisites are fulfilled regarding product composition and in vitro dissolution (see also Section IV.2 Excipients). The more restrictive requirements will also apply for compounds proposed to be BCS class I but where complete absorption could not convincingly be demonstrated.

Reported bioequivalence between aqueous and solid formulations of a particular compound administered via the oral route may be supportive as it indicates that absorption limitations due to (immediate release) formulation characteristics may be considered negligible. Well performed in vitro permeability investigations including reference standards may also be considered supportive to in vivo data.

IV. Finished pharmaceutical product

IV.1 In vitro Dissolution

IV.1.1 General Aspects

Investigations related to the medicinal product should ensure immediate release properties and prove similarity between the investigative products, i.e. test and reference show similar in vitro dissolution under physiologically relevant experimental pH conditions. However, this does not establish an in vitro/in vivo correlation. In vitro dissolution should be investigated within the range of pH 1 – 6.8 (at least pH 1.2, 4.5, and 6.8). Additional investigations may be required at pH values in which the drug substance has minimum solubility. The use of any surfactant is not acceptable.

Test and reference products should meet requirements as outlined in Section 3.1.2 of the main guideline text. In line with these requirements, it is advisable to investigate more than one single batch of the test and reference products.

Comparative in vitro dissolution experiments should follow current compendial standards. Hence, thorough description of experimental settings and analytical methods including validation data should be provided. It is recommended to use 12 units of the product for each experiment to enable statistical evaluation. Usual experimental conditions are e.g.:-

Apparatus: paddle or basket

Volume of dissolution medium: 900 ml or less

Temperature of the dissolution medium: 37±1 °C

Agitation:

- paddle apparatus - usually 50 rpm
- basket apparatus - usually 100 rpm

Sampling schedule: e.g. 10, 15, 20, 30 and 45 min

Buffer: pH 1.0 – 1.2 (usually 0.1 N HCl or SGF without enzymes), pH 4.5, and pH 6.8 (or SIF without enzymes); (pH should be ensured throughout the experiment; Ph.Eur. buffers recommended)

Other conditions: no surfactant; in case of gelatin capsules or tablets with gelatin coatings the use of enzymes may be acceptable.

Complete documentation of in vitro dissolution experiments is required including a study protocol, batch information on test and reference batches, detailed experimental conditions, validation of experimental methods, individual and mean results and respective summary statistics.

IV.1.2 Evaluation of in vitro dissolution results

Finished pharmaceutical products are considered 'very rapidly' dissolving when more than 85 % of the labelled amount is dissolved within 15 min. In cases where this is ensured for the test and reference product the similarity of dissolution profiles may be accepted as demonstrated without any mathematical calculation.

Absence of relevant differences (similarity) should be demonstrated in cases where it takes more than 15 min but not more than 30 min to achieve almost complete (at least 85 % of labelled amount) dissolution. *F2*-testing (see Annex X) or other suitable tests should be used to demonstrate profile similarity of test and reference. However, discussion of dissolution profile differences in terms of their clinical/therapeutical relevance is considered inappropriate since the investigations do not reflect any *in vitro/in vivo* correlation.

IV.2 Excipients

Although the impact of excipients in immediate release dosage forms on bioavailability of highly soluble and completely absorbable active pharmaceutical ingredients (i.e., BCS-class I) is considered rather unlikely it cannot be completely excluded. Therefore, even in the case of class I drugs it is advisable to use similar amounts of the same excipients in the composition of test like in the comparator product.

If a biowaiver is applied for a BCS-class III active pharmaceutical ingredient excipients have to be qualitatively the same and quantitatively very similar in order to exclude different effects on membrane transporters.

As a general rule, for both BCS-class I and III active pharmaceutical ingredients well-established excipients in usual amounts should be employed and possible interactions affecting drug bioavailability and/or solubility

characteristics should be considered and discussed. A description of the function of the excipients is required with a justification whether the amount of each excipient is within the normal range. Excipients that might affect bioavailability, like e.g. sorbitol, mannitol, sodium lauryl sulfate or other surfactants, should be identified as well as their possible impact on:-

- gastrointestinal motility
- susceptibility of interactions with the active pharmaceutical ingredient (e.g. complexation)
- drug permeability
- interaction with membrane transporters

Excipients that might affect bioavailability should be qualitatively and quantitatively the same in the test product and the comparator product.

V. Fixed Combinations (FCs)

BCS-based biowaiver are applicable for immediate release FC products if all active substances in the FC belong to BCS-class I or III and the excipients fulfil the requirements outlined in Section IV.2. Otherwise, in vivo bioequivalence testing is required.

Annex XIII: Biopharmaceutics Classification System (BCS)

Biowaiver Application Form:

This application form is designed to facilitate information exchange between the Applicant and the PPB National Medicines Regulatory Authorities (PPBs) if the Applicant seeks to waive bioequivalence studies based on the Biopharmaceutics Classification System (BCS). For further information, please study the respective PPB biowaiver guidance documents. This form is not to be used if a biowaiver is requested for additional strength(s) of a submitted product(s), in which case a separate "Biowaiver Application Form: Additional Strengths" should be used.

The PPB Product and Evaluation Department has identified some Active Pharmaceutical Ingredients (APIs) that are eligible for a BCS-based biowaiver application. For those APIs, it may not necessary to provide data to support the BCS classification of the respective API(s) in the application i.e., data supporting the drug substance solubility or absorption/permeability class.

General Instructions:

Please review all the instructions thoroughly and carefully prior to completing the current Application Form.

- Provide as much detailed, accurate, and final information as possible.
- Please enter the data and information directly following the greyed areas.
- Please enclose the required documentation in full and state in the relevant sections of the Application Form the exact location (Annex number) of the appended documents. For example, in section 2.5 indicate in which Annex the Certificate of Analysis can be found.
- Please provide the document as an MS Word file.
- Do not paste snap-shots into the document.

- The appended electronic documents should be clearly identified in their file names, which should include the product name and Annex number.
- Before submitting the completed Application Form, kindly check that you have provided all requested information and enclosed all requested documents.
- Should you have any questions regarding this procedure, please contact pharmacy and Poisons Board).

The signed paper version of this Biowaiver Application Form together with Annexes should be included to the bioequivalence part of the submitted dossier

Administrative data

1. INN of active ingredient(s)
<< *Please enter information here* >>

2. Dosage form and strength
<<*Please enter information here* >>

3. Product PPB Reference number *(if product dossier has been accepted by PPB for assessment)*
<< *Please enter information here* >>

4. Name of applicant and official address
<< *Please enter information here* >>

5. Name of manufacturer of finished product and official address
<< *Please enter information here* >>

6. Name and address of the laboratory or Contract Research Organisation(s) where the BCS-based biowaiver solubility and dissolution studies were conducted
<< *Please enter information here* >>

I, the undersigned, certify, that the information provided in this application and the attached documents is correct and true

Signed on behalf of

<Company>

_____ (Date)

_____ (Name and title)

Section 1: Justification for a BCS Biowaiver

1.1 Active Pharmaceutical Ingredient (API) Please confirm that the proposed product contains the same active substance (e.g. salt, ester, ether, isomer) as the comparator.
<< Please enter information here >>

1.2 Therapeutic Index of the API Please enclose a copy of the comparator product labelling and literature references employed to support that the drug does not exhibit a narrow therapeutic index for all authorised indications
<< Please enter information here >>

1.3 Pharmacokinetic properties of the API Please enclose a copy of the literature references employed to document the PK properties (PK linearity or reasons for non-linearity).
<< Please enter information here >>

1.4 Dosage form
Please confirm that: ☐ the dosage form is an immediate release product for systemic action ☐ the posology is limited to oral administration ☐ the administration without water is not included in the proposed posology
<< Please enter information here >>

1. COMMENTS FROM REVIEW OF SECTION 1 – *PPB USE ONLY*

Section 2: Solubility

(Completion of this section is not necessary if the API(s) are included on the list of biowaiver-eligible APIs in the *General notes on Biopharmaceutics Classification System (BCS)-based biowaiver applications*.)

2.1. Maximum therapeutic dose of the API Please enclose a copy of the labelling of the comparator product to document the maximum single dose that can be administered in a single administration (e.g. two tablets together).

<< *Please enter information here* >>

2.2.Stability of the drug in the physiological pH range
Please discuss stability of the API in the pH range from 1.2 to 6.8 and in the gastrointestinal tract.
Please discuss the ability of the analytical method to distinguish the API from its degradation products.

<< *Please enter information here* >>

2.3.Method of solubility determination
Please describe method and conditions (e.g. shake flask method at 37±1°C)
Please indicate also location of the solubility study protocol.

<< *Please enter information here* >>

2.4.Solubility study dates
Please indicate dates of study protocol, study conductance and study report

<< *Please enter information here* >>

2.5. Analytical method validation
Please summarise the results and indicate location in the documentation.

<< *Please enter information here* >>

2.6. Results
Please indicate location of the solubility study report.
Please fill in the following table for the necessary pH values. Add as many rows as necessary to create a solubility – pH profile

Theoretical pH	Observed pH	Adjusted pH	Individual concentration at saturation (Cs) values	Cs (mean and CV(%))	Amount that can be dissolved in 250 mL
pH 1.2	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3		
Intermdiate pHs	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3		
pH 4.5	Experiment 1	Experiment 1	Experiment 1 Experiment 2 Experiment 3		

	Experiment 2 Experiment 3	Experiment 2 Experiment 3			
Intermediate pHs	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3		
pH 6.8	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3		
Other intermediate pH values (e.g. pKa, pKa-1, pKa+1)	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3		

2.7.Plot the Solubility – pH profile Please attach the plot of the pH-solubility profile based on the above data
<< Please enter information here >>

3.0 COMMENTS FROM REVIEW OF SECTION 2 – *PPB USE ONLY*

Annex XIV: Selection of a comparator product to be used in establishing interchangeability

I. Introduction

This annex is intended to provide applicants with guidance with respect to selecting an appropriate comparator product to be used to prove therapeutic equivalence (i.e. interchangeability) of their product to an existing medicinal product(s) in the context of the PPB Medicines Registration Harmonization programme.

II. Comparator product

A product with which a generic product is intended to be interchangeable in clinical practice.

III. Guidance on selection of a comparator product

General principles for the selection of comparator products are described by EAC guidelines on therapeutic equivalence requirements, First Edition, 2014.

The innovator pharmaceutical product, which was first authorized for marketing, is the most logical comparator product to establish interchangeability, because its quality, safety and efficacy has been fully assessed and documented in pre-marketing studies and post-marketing monitoring schemes.

A generic pharmaceutical product should not be used as a comparator as long as an innovator pharmaceutical product is available, because this could lead to progressively less reliable similarity of future multisource products and potentially to a lack of interchangeability with the innovator.

Comparator products should be purchased from a well regulated market with stringent regulatory authority, i.e. from countries participating in the International Conference on Harmonization (ICH)1

In the context of the PPB the applicant has the following options which are listed in order of preference:

a) To choose an innovator product;

b) To choose a product which is approved and has been on the market in any of the SRA countries. The definition of an SRA is rephrased as follows. A regulatory authority that is: a)a member of ICH prior to 23 October 2015, namely: the US Food and Drug Administration, the European Commission and the Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency; orb)an ICH observer prior to 23 October 2015, namely: the European Free Trade Association, as represented by Swissmedic and Health Canada; orc)a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement prior to 23 October 2015, namely: Australia, Iceland, Liechtenstein and Norway

c) To choose the WHO recommended comparator product (as presented in the list of international comparator pharmaceutical products);

In case no recommended comparator product is identified; or in case the PPB recommended comparator product cannot be located in a well-regulated market with stringent regulatory authority as noted above, the applicant should consult the PPB regarding the choice of comparator before starting any studies.

IV. Origin of the comparator product

Comparator products should be purchased from a well-regulated market with stringent regulatory authority, i.e. from countries participating in the International Conference on Harmonization (ICH)1. Within the submitted dossier, the country of origin of the comparator product should be reported together with lot number and expiry date, as well as results of pharmaceutical analysis to prove pharmaceutical equivalence.

Further in order to prove the origin of the comparator product the applicant must present all of the following documents: -

1. Copy of the comparator product labelling. The name of the product, name and address of the manufacturer, batch number, and expiry date should be clearly visible on the labelling.

2. Copy of the invoice from the distributor or company from which the comparator product was purchased. The address of the distributor must be clearly visible on the invoice.
3. Documentation verifying the method of shipment and storage conditions of the comparator product from the time of purchase to the time of study initiation.
4. A signed statement certifying the authenticity of the above documents and that the comparator product was purchased from the specified national market. The certification should be signed by the company executive responsible for the application for registration of pharmaceutical product.

In case the invited product has a different dose compared to the available acceptable comparator product, it is not always necessary to carry out a bioequivalence study at the same dose level; if the active substance shows linear pharmacokinetics, extrapolation may be applied by dose normalization.

The bioequivalence of fixed-dose combination (FDC) should be established following the same general principles. The submitted FDC product should be compared with the respective innovator FDC product. In cases when no innovator FDC product is available on the market, individual component products administered in loose combination should be used as a comparator.

Countries officially participating in ICH are the ICH members European Union, Japan and USA; and the ICH observers Canada and Switzerland.

REFERENCES

1. WHO guideline on bioequivalence studies.
2. India draft guideline for bioavailability and bioequivalence studies.
3. EMA guideline on the investigation of bioequivalence.
4. JP NIHS guideline for bioequivalence studies for different strengths of oral solid dosage forms.

5. Bioequivalence Implementation Framework/Roadmap

PART IV:

COMMON GLOSSARY OF TERMS USED IN MEDICINES REGISTRATION

1. INTRODUCTION

The Glossary of Terms in medicines registration has been developed to minimize misunderstanding of words used in medicines registration as this process is at the nexus of many key stakeholders. There is also an increasing proliferation and duplication of terms and definitions, as the medicines registration field itself is still evolving and adapting itself to new and changing contexts.

The glossary provides information on the range of terms and definitions encountered in medicines registration. It does not present new or different definitions of terms, but draws together definitions from many existing sources. Changes to definitions have been minimal, and only made to unify the style of the Glossary, e.g. some spelling has been standardised, and the plural form of terms has been replaced by the singular form.

2. SELECTION OF TERMS

The terms were selected from existing glossaries appended to the EAC guidelines., The terms were also selected from international guidelines such as USFDA, WHO, EMA, Health Canada and other international publications.

Furthermore, definitions were selected using the criteria of widespread acceptance and widespread.

3. GLOSSARY

In the context of Product Evaluation and Registration, the following words/phrases are defined as follows:

Active pharmaceutical ingredient (API)	An active ingredient is any component that provides pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or animals. *(USFDA Glossary of terms, it can be found in line at Drugs@FDA Glossary of Terms).*
Acceptance criteria	The product specifications and acceptance/rejection criteria, such as acceptable quality level and unacceptable quality level, with an associated sampling plan, that are necessary for making a decision to accept or reject a lot or batch (or any other convenient subgroups of manufactured units). (WHO guide to good manufacturing practice (GMP) requirements, at http://www.who.int/vaccines-documents/DocsPDF/www9651.pdf).
Active Pharmaceuti	See Drug Master File (DMF)

cal Ingredient Master File-(APIMF)	
Active Substance	See Active pharmaceutical ingredient (API)
Adverse reaction (Adverse Drug Reaction, ADR)	An adverse drug reaction is a response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function. At:http://www.who.umc.org/DynPage.aspx?id=13111&mn=1513]
Applicant	See Marketing Authorization Holder
Batch (or lot)	A defined quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. (European Federation of Pharmaceutical Industries and Association; GMP for API manufacturer, at http://apic.cefic.org/pub/1gmp-api9604.pdf).
Batch number (or lot number)	A distinctive combination of numbers and/or letters which specifically identifies a batch or lot and from which the production history can be determined. (European Federation of Pharmaceutical Industries and Association; GMP for API manufacturer, at http://apic.cefic.org/pub/1gmp-api9604.pdf).
Bio-equivalence	The absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of action when administered at the same molar dose under similar conditions in an appropriately designed study. (Glossary (terms and abbreviations)/EMA).
Bulk product	Any product that has completed all processing stages up to, but not including, final packaging. (WHO guide to good manufacturing practice (GMP) requirements, at http://www.who.int/vaccines-documents/DocsPDF/www9651.pdf).
Calibration	A set of operations which establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by a material measure, and the corresponding known values of a reference standard. (European Federation of Pharmaceutical Industries and Association; GMP for API manufacturer, at http://apic.cefic.org/pub/1gmp-api9604.pdf).
Certificate of Pharmaceutical Product (CPP)	WHO-type certificate as defined in the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce. (WHO Model Quality Assurance System for Procurement Agencies; it can be found at http://www.myaccessrh.org/documents/10157/37547/ModelQualityAssurance.pdf).
Clinical trial (clinical study)	A clinical trial is any systematic study on pharmaceutical products in human subjects, whether in patients or other volunteers, in order to discover or verify the effects of, and/or identify any adverse reaction to, investigational products, and/or to study the absorption, distribution, metabolism and excretion of the products with the object of ascertaining their efficacy and safety. (WHO Medicines Regulatory Package. A Collection of Tools for Medicines Regulatory Authorities - Regulatory Support Series No. 014 at: http://infocollections.org/medregpack/interface/files/glossary.pdf)
Comparator	An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.

	(http://www.gcphelpdesk.com/index.php/glossary/10-c)
Comparator product	A pharmaceutical product with which the multisource product is intended to be interchangeable in clinical practice (https(://www.who.int/medicines/areas/quality_safety/quality_assurance/guidanceontheselectionofcomparatorpharmproducts-etc_qas14-596_18072014.pdf)
Composition	Composition in relation to a medicinal product means the ingredients of which it consists, proportions, degree of strength, quality and purity in which those ingredients are contained. Kenya and Guidelines on submission for Documentation for Registration of Human medicinal Product-TFDA).
Conditional Authorization	This is authorization granted by the National regulatory Authority that allows for continued clinical studies post Authorization e.g. for pivotal Phase IV studies. The Licence is renewable every two years as per Cap 244 Laws of Kenya.
Conflict of interest	A conflict of interest is a situation in which a public official's decisions are influenced by the official's personal interests. [At: http://wordnet.princeton.edu/]
Contamination	The unintended, non-process related, introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a material during production, sampling, packaging or repackaging, storage or transport. (European Federation of Pharmaceutical Industries and Association; GMP for API manufacturer, at http://apic.cefic.org/pub/1gmp-api9604.pdf).
Continuous production	A process in which a material is continuously produced in a step or series of steps. In a continuous process the batches of raw materials and the process parameters can be statistically, but not absolutely, correlated to the material produced in a given window of time. (European Federation of Pharmaceutical Industries and Association; GMP for API manufacturer, at http://apic.cefic.org/pub/1gmp-api9604.pdf).
Controlled Medicines	Narcotic medicines and psychotropic substances regulated by provisions of national medicines laws. (WHO Medicines Regulatory Package. A Collection of Tools for Medicines Regulatory Authorities - Regulatory Support Series No. 014 at: http://infocollections.org/medregpack/interface/files/glossary.pdf)
Cross contamination	Contamination of a material or product with another material or product, thus cross contamination is a particular form of contamination. (European Federation of Pharmaceutical Industries and Association; GMP for API manufacturer, at http://apic.cefic.org/pub/1gmp-api9604.pdf).
Data exclusivity	Data exclusivity is the protection of an originator pharmaceutical company's data preventing other parties from using these data for a commercial purpose. (OECD – Pharmaceutical Pricing Policies in a Global Market, at: http://www.oecd.org/document/36/0,3343,en_2649_33929_41000996_1_1_1_37407,00.html).
Design Space	The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. (ICHQ8- Glossary at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002872.pdf)
Direct to consumer advertising	Direct-to-consumer advertising (DTC advertising) usually refers to the marketing of medicines aimed directly toward the public, rather than healthcare professionals. Forms of DTC advertising include TV, print, and radio.

	(OECD – Pharmaceutical Pricing Policies in a Global Market, at: http://www.oecd.org/document/36/0,3343,en_2649_33929_41000996_1_1_1_37407,00.html).
Distribution category	Distribution category indicates how a drug product is sold or dispensed. For example Prescription Only Medicines (POM), Over the Counter (OTC refer to national guideline).(WHO glossary of terms)
Dosage form	See pharmaceutical form
Drug Master File (DMF)	Is a master file that provides a full set of data on an active pharmaceutical ingredient (API). In other circumstances the term may also comprise data on an excipient. (Guidelines to Submission of Applications for Registration of Drug, Pharmacy and Poisons Board-Kenya).
Drug Product	A finished dosage form, for example, a tablet, capsule or solution that contains an active pharmaceutical ingredient, generally, but not necessarily, in association with inactive ingredients. Reference: Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients FDA Guidance (https://www.registrarcorp.com/fdadrugs/definitions/)
Drug Substance	See Active pharmaceutical ingredient (API)
Duplicate license	Marketing authorization issued to a product that is identical in terms of qualitative and quantitative composition, manufacturing process and sites as well as quality controls to an already registered medicinal product. The only difference would be the brand name and product labels.
Efficacy	The ability of a drug to produce the intended effect as determined by scientific methods, for example in pre-clinical research or clinical research studies. (WHO Glossary of terms used in Pharmacovigilance, at http://who-umc.org/Graphics/24729.pdf).
Emergency Use Authorization	Emergency use means approval for use when public health emergency has been declared i.e. the use of a medicine (therapeutic), vaccine, or in vitro diagnostic or medical device) on patients in a life-threatening situation or condition, including chemical, radiologic or nuclear attack, in which no standard treatment or diagnostic is available, and in which there is no sufficient time to obtain product registration. Emergency use authorization procedure may also be applied in extreme situations such as during war. Refer to “Guidelines for Emergency and Compassionate Use Authorization of Health Products and Technologies, April 2020”.
Essential medicines	Essential medicines satisfy the priority health care needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness. (At: http://www.who.int/topics/essential_medicines/en/)
Ethics Committee (EC)/ Institutional Review Board (IRB)	Ethics Committees (EC) ensure that biomedical research follows international guidelines, including the Declaration of Helsinki, the WHO and ICH Guidelines for Good Clinical Practice. The purpose of an EC in reviewing biomedical research is to contribute to safeguarding the dignity, rights, safety, and well-being of all actual or potential research participants. (Operational Guidelines for Ethics Committees That Review Biomedical Research Geneva 2000, can be found online at: http://apps.who.int/tdr/publications/training-guideline-publications/operational-guidelines-ethics-biomedical-research/pdf/ethics.pdf)
Excipient	Is any constituent of a pharmaceutical form that is not an active pharmaceutical ingredient

	(Guideline on excipients in the dossier for application for marketing authorization of a medicinal product, it can be found on line at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003380.pdf).
Extension application	A new application that is a modification/addition to an already registered medicinal product. The modification/addition shall be such that it does not fulfil criteria for minor or major variations but is similar enough to the original (already registered) product in terms of quality, safety and efficacy. A new marketing authorization will be issued for extension applications
Finished Pharmaceutical Product (FPP)	A finished dosage form of a pharmaceutical product which has undergone all stages of manufacture, including packaging in its final container and labelling (WHO Glossary)
Formulary	A formulary is a manual containing clinically oriented summaries of pharmacological information about selected medicines. (How to develop a national formulary based on the WHO model formulary, a practical guide Geneva 2004, can be found online at: http://apps.who.int/medicinedocs/en/d/Js6171e/2.3.html)
General Sales Medicines (GSM)	Medicines which may be sold either by way of retail or wholesale in an open shop such as supermarkets.
Generic product	Is a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. (PHIS Glossary 2009, can be found on line at: http://phis.goeg.at/index.aspx?alias=phisglossary)
Good Clinical Practice	A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected. (PHIS Glossary 2009, can be found on line at: http://phis.goeg.at/index.aspx?alias=phisglossary
Good Manufacturing Practice (GMP)	Part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization. (WHO A model quality assurance system for procurement agencies Geneva 2007, can be found online at: http://apps.who.int/medicinedocs/documents/s14866e/s14866e.pdf)
Impurity	Any component present in the active pharmaceutical ingredient other than the substance defined as the active pharmaceutical ingredient (European Federation of Pharmaceutical Industries and Association; GMP for API manufacturer, At http://apic.cefic.org/pub/1gmp-api9604.pdf).
Innovator medicinal product	Generally the medicinal product that was first authorized for marketing (normally as a patented product) on the basis of documentation of efficacy, safety and quality. (WHO glossary of terms) (Adapted from WHO glossary of terms)
In-process control	Checks performed during production in order to monitor and, if necessary, to adjust the process, including repeating a process step, to ensure that the product conforms to its specification. (European Federation of Pharmaceutical Industries and Association; GMP for API manufacturer, at http://apic.cefic.org/pub/1gmp-api9604.pdf).

Intermediate	Partly processed material which must undergo further production steps before it becomes an Active Ingredient. (European Federation of Pharmaceutical Industries and Association; GMP for API manufacturer, at http://apic.cefic.org/pub/1gmp-api9604.pdf).
International Conference on harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)	The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration. [At: http://www.ich.org/cache/compo/276-254-1.html]
Reference product	Pharmaceutical product with which the new product is intended to be interchangeable in clinical practice. The reference product will normally be the innovator product for which efficacy, safety and quality have been established. Where the innovator product is not available, the product which is the market leader may be used as a reference product, provided that it has been authorized for marketing and its efficacy, safety and quality have been established and documented. (http://apps.who.int/medicinedocs/en/d/Js5516e/19.2.html#Js5516e.19.2)
International Non-proprietary Name (INN)	INN is a unique name that is globally recognized and is public property. [WHO Guidance on INN at: http://www.who.int/medicines/services/inn/innguidance/en/index.html]
Label	Is a descriptive matter, written, printed, stenciled, marked, embossed or impressed on or attached to a packaging of any medicinal product. (Adapted from USFDA Glossary of terms, can be found in line at Drugs@FDA Glossary of Terms).
Law	Laws define the roles, rights and obligations of all parties involved in the subject matter in general terms. (WHO Medicines Regulatory Package. A Collection of Tools for Medicines Regulatory Authorities - Regulatory Support Series No. 014 at: http://infocollections.org/medregpack/interface/files/glossary.pdf)
Legal category	See Distribution category
Legislation	Legislation corresponds to the first stage of the legislative process, in which laws are passed by the legislative body of government with regard to a subject matter such as the control of pharmaceuticals. (WHO A model quality assurance system for procurement agencies Geneva 2007, can be found online at: http://apps.who.int/medicinedocs/documents/s14866e/s14866e.pdf)
License Holder	A license holder is an individual or a corporate entity possessing a marketing authorization for a medicinal product. (WHO Medicines Regulatory Package. A Collection of Tools for Medicines Regulatory Authorities - Regulatory Support Series No. 014 at: http://infocollections.org/medregpack/interface/files/glossary.pdf) (Also see Market Authorization Holder).
Licensing system	National legal provisions on who should manufacture, import or supply medicinal products, what qualifications people in the supplying agency

	should have, and who should dispense and sell pharmaceutical products. (WHO glossary of terms)
Local Technical Representative	A person or company with sufficient pharmaceutical expertise that is incorporated within the specific country and who will be responsible for facilitating communication with the Applicant and when the product is registered shall assume all legal responsibilities.
Manufacture (manufacturing)	Manufacturing includes all operations of receipt of materials, production, packaging, repackaging, labelling, relabeling, quality control, release, storage and distribution of active pharmaceutical ingredients and/or medicinal product. [PHIS Glossary 2009, can be found on line at: http://phis.goeg.at/index.aspx?alias=phisglossary]
Manufacturer	A manufacturer is a natural or legal person with responsibility for manufacturing of a medicinal product or active pharmaceutical ingredient. (PHIS Glossary 2009, can be found on line at: http://phis.goeg.at/index.aspx?alias=phisglossary)
Market Authorization Holder	Marketing Authorization Holder, is an entity or organization responsible for obtaining and holding the marketing authorization for a medicinal product in a specific geographical region, such as a country or a group of countries. The MAH is the party that has the legal and regulatory responsibility for the authorization, distribution, and marketing of the product within the designated region.
Marketing Authorization (MA)	Means approval to market a medicinal product in Kenya (Glossary of terms and abbreviations/EMA, it can be found at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/12/WC500099907.pdf).
Medical device	Means an article which is intended to be used for human beings or animals for the purpose of diagnosis, prevention, monitoring, treatment or alleviation of disease, diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap, investigation, replacement or modification of the anatomy or of a physiological process, or control of conception and does not achieve its purpose by pharmacological, immunological or metabolic means. (Upholding standards and public trust in pharmacy, at http://www.pharmacyregulation.org/sites/default/files/Glossary%20of%20terms%20used%20in%20GPhC%20standards%20Feb%202012.pdf)
Medicinal Product	Any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, prevention, correcting or modifying physiological functions in human beings or animals.
Medicinal Substance	See Active pharmaceutical ingredient (API)
Medicines Regulatory Authority	A national body that has the legal mandate to set objectives and administer the full spectrum of medicines regulatory activities. (WHO Medicines Regulatory Package. A Collection of Tools for Medicines Regulatory Authorities - Regulatory Support Series No. 014 at: http://infocollections.org/medregpack/interface/files/glossary.pdf).
National essential medicines list	The list of essential medicines that has been defined, adopted, and published at country level. (WHO A model quality assurance system for procurement agencies Geneva 2007, can be found online at: http://apps.who.int/medicinedocs/documents/s14866e/s14866e.pdf)
Originator medicinal	An originator brand is generally the product that was first authorized worldwide for marketing (normally as a patented product) on the basis of

product/originator brand	the documentation of its efficacy, safety and quality, according to requirements at the time of authorization. (HAI/WHO Measuring medicine prices, availability, affordability and price components (2nd Edition) and at: http://www.haiweb.org/medicineprices/manual/documents.html)
Over-The-Counter medicines (OTC)	Are medicines which are safe and effective for use by the general public without a doctor's prescription. (WHO Medicines Regulatory Package. A Collection of Tools for Medicines Regulatory Authorities Regulatory Support Series No. 014 at: http://infocollections.org/medregpack/interface/files/glossary.pdf)
Packaging materials	Any material used to protect an Active Pharmaceutical Ingredient or finished pharmaceutical product during storage and transport but excluding labels.(European Federation of Pharmaceutical Industries and Association; GMP for API manufacturer, at http://apic.cefic.org/pub/1gmp-api9604.pdf).
Patient Information Leaflet (PIL)	Packages insert which contains information for patient's understanding of how to safely use a medicinal product. (USFDA Glossary of terms, can be found in line at Drugs@FDA Glossary of Terms).
Pharmaceutical alternatives	Medicinal products are considered pharmaceutical alternatives if they contain the same therapeutic moiety, but are different salt, esters, or complexes of that moiety, or are different dosage forms or strengths. (USFDA Orange book, it can be found on line at http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4137B1_07_Nomenclature.pdf)
Pharmaceutical equivalents	Medicinal products are considered to be pharmaceutical equivalents if they contain the same active ingredient(s) same dosage form and route of administration and they are identical in strength or concentration. (USFDA Glossary of terms, can be found in line at Drugs@FDA Glossary of Terms)
Pharmaceutical form	The pharmaceutical form is the pharmaceutical-technological form in which an active substance is made available. Pharmaceutical may be administered in solid form (e.g. tablets, powers), in semi-liquid form (e.g. ointments, pastes), in liquid form (e,g, drops, injectables, infusions) or in gaseous form (inhalation). (WHO glossary of terms).
Pharmaceutical Product	A pharmaceutical product is any substance for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient. [WHO A model quality assurance system for procurement agencies Geneva 2007, can be found online at: http://apps.who.int/medicinedocs/documents/s14866e/s14866e.pdf]
Pharmacy	Pharmacies are premises which in accordance to the local legal provisions and definitions may operate as a facility in the provision of pharmacy services in the community or health facility setting. (In WHO Operational package for assessing, monitoring and evaluating country pharmaceutical situations at: http://www.who.int/medicines/publications/WHO_TCM_2007.2/en/)
Post-marketing surveillance	Post-marketing surveillance is testing medicine samples to assess the quality of medicines that have already been licensed for public use. (In WHO Operational package for assessing, monitoring and evaluating country pharmaceutical situations at: http://www.who.int/medicines/publications/WHO_TCM_2007.2/en/)
Post-marketing surveillance study	Studies performed after the pharmaceutical product has been marketed. (In WHO Operational package for assessing, monitoring and evaluating country pharmaceutical situations at: http://www.who.int/medicines/publications/WHO_TCM_2007.2/en/)

Pre-marketing	The stage before a drug is available for prescription or sale to the public.(WHO Glossary of terms used in Pharmacovigilance, At http://who-umc.org/Graphics/24729.pdf.
Prescription-Only Medicines	Prescription-only medicines are medicines supplied only in licensed pharmacies on the presentation of signed prescriptions issued by a licensed and registered medical practitioner, licensed and/or registered dentist (for dental treatment only), and/or licensed and/or registered veterinarian (for animal treatment only), and the supply and dispensing of these medicines must be carried out by a pharmacist or under the supervision of a pharmacist. (WHO glossary of terms)
Procedures	Description of the operations to be carried out, the precautions to be taken, and measures to be applied directly or indirectly related to the manufacture of an Active Ingredient and Finished Pharmaceutical product. (European Federation of Pharmaceutical Industries and Association; GMP for API manufacturer, at http://apic.cefic.org/pub/1gmp-api9604.pdf).
Process aids	Materials used as aids in the manufacture of an Active Ingredient and Finished Pharmaceutical Product which themselves do not participate in a chemical or biological reaction. (Federation of Pharmaceutical Industries and Association; GMP for API manufacturer, at http://apic.cefic.org/pub/1gmp-api9604.pdf).
Product Information	Product information refers to the summary of product characteristics (SmPC), labelling and patient information leaflet. (Glossary of terms and abbreviations/EMA it can be found at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/12/WC500099907.pdf).
Promotion	Promotion refers to all informational and persuasive activities by manufacturers and distributors, the effect of which is to induce the prescription, supply, purchase and/or use of medicinal drugs. [C:\Documents and Settings\CVialle\Desktop\Country profile - Instructions and glossary 14 Sept 2010\WHO. A model quality assurance system for procurement agencies.pdf Criteria for Medicinal Drug Promotion can be found online at: http://apps.who.int/medicinedocs/documents/whozip08e/whozip08e.pdf]
Proprietary name	Name given for marketing purposes to any ready-prepared medicine placed on the market. (PHIS Glossary 2009, it can be found at http://phis.goeg.at/downloads/glossary/PHIS%20Glossary_UpdatedApril2011.pdf).
Quality Information Summary (QIS)	The QIS is a condensed version of the Quality Overall Summary – Product Dossier (QOS-PD) and represents the final, agreed upon key information from the PD review (inter alia identification of the manufacturer(s), API/FPP specifications, stability conclusions and relevant commitments)
Qualification	The action of proving that any equipment is properly installed, works correctly, and consistently produces the expected results. Qualification is part of, but not limited to, the validation process. (Federation of Pharmaceutical Industries and Association; GMP for API manufacturer, at http://apic.cefic.org/pub/1gmp-api9604.pdf).
Quality assurance	It is the sum total of the organized arrangements made with the object of ensuring that Active Ingredients and Finished Pharmaceutical products are of the quality required for their intended use. (Federation of Pharmaceutical Industries and Association; GMP for API manufacturer, at http://apic.cefic.org/pub/1gmp-api9604.pdf).
Quality attribute	Any product characteristic which may reflect quality, or may affect safety or efficacy of the product during its expected shelf life.

	(Federation of Pharmaceutical Industries and Association; GMP for API manufacturer, at http://apic.cefic.org/pub/1gmp-api9604.pdf).
Quality Control	Quality control is the part of Good Manufacturing Practices (GMP) concerned with sampling, specifications, and testing and with the organization, documentation, and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use or products released for sale or supply, until their quality has been judged to be satisfactory. (WHO Medicines Regulatory Package. A Collection of Tools for Medicines Regulatory Authorities - Regulatory Support Series No. 014 at: http://infocollections.org/medregpack/interface/files/glossary.pdf).
Quarantine	The status of materials isolated physically or by other effective means whilst awaiting a decision on their subsequent use. (Federation of Pharmaceutical Industries and Association; GMP for API manufacturer, at http://apic.cefic.org/pub/1gmp-api9604.pdf).
Rational use of medicines	Rational use of medicines requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community. (Promoting rational use of medicines: Core components Geneva 2002, can be found online at: http://apps.who.int/medicinedocs/pdf/h3011e/h3011e.pdf)
Raw materials	Any material of defined quality used in the manufacture of an Active Ingredient, but excluding packaging materials or labels. (European Federation of Pharmaceutical Industries and Associations; April 1996, Good manufacturing practices for Active ingredient manufacturers).
Recovery	Any treatment of materials by a process intended to make them suitable for further use. (Federation of Pharmaceutical Industries and Association; GMP for API manufacturer, at http://apic.cefic.org/pub/1gmp-api9604.pdf).
Registration	See Marketing Authorization
Regulations	The second stage of the legislative process (the first stage being legislation). Regulations are specifically designed to provide the legal machinery to achieve the administrative and technical goals of legislation. (WHO A model quality assurance system for procurement agencies Geneva 2007, can be found online at: http://apps.who.int/medicinedocs/documents/s14866e/s14866e.pdf)
Regulatory Inspection	A regulatory inspection is an officially conducted examination (i.e. review of quality assurance processes, personnel involved, any delegation of authority and audit) by relevant authorities at sites where pharmaceutical activities take place (i.e. manufacturing, wholesale, testing, distribution, clinical trials) to verify adherence to Good Practices. (WHO Medicines Regulatory Package. A Collection of Tools for Medicines Regulatory Authorities - Regulatory Support Series No. 014 at: http://infocollections.org/medregpack/interface/files/glossary.pdf)
Reprocessing	The treatment of a batch or sub-batch of materials of unacceptable quality by repeating the same process steps from a defined stage of production so that its quality may be made acceptable. (Federation of Pharmaceutical Industries and Association; GMP for API manufacturer, at http://apic.cefic.org/pub/1gmp-api9604.pdf).
Reworking	The treatment of a batch or sub-batch of materials of unacceptable quality by using a process other than that used to produce the original material so that its quality may be made acceptable. (Federation of Pharmaceutical Industries and Association; GMP for API manufacturer, at http://apic.cefic.org/pub/1gmp-api9604.pdf).

Route of administration	Is a way of administering a medicinal product to a site in a patient. (USFDA Glossary of terms, can be found on line at Drugs@FDA Glossary of Terms).
Sample	A sample is a portion of a material collected according to a defined sampling procedure. WHO Medicines Regulatory Package. A Collection of Tools for Medicines Regulatory Authorities - Regulatory Support Series No. 014 at: http://infocollections.org/medregpack/interface/files/glossary.pdf]
Sampling	Operations designed to obtain a representative portion of a pharmaceutical product, based on an appropriate statistical procedure, for a defined purpose, e.g. acceptance of consignments, batch release. (WHO Medicines Regulatory Package. A Collection of Tools for Medicines Regulatory Authorities - Regulatory Support Series No. 014 at: http://infocollections.org/medregpack/interface/files/glossary.pdf)
Side effect	Any unintended effect of a pharmaceutical product occurring at normal dosage which is related to the pharmacological properties of the drug. (WHO Glossary of terms used in Pharmacovigilance, at http://who-umc.org/Graphics/24729.pdf)
Specifications	A document describing in detail the requirements such as physical, chemical, biological and microbiological test requirements with which the products or materials used or obtained during manufacture have to conform. (A WHO guide to good manufacturing practice (GMP) requirements; it can be found at http://www.who.int/vaccinesdocuments/DocsPDF/www9651.pdf).
Specifications	Test Procedures and Acceptance Criteria for active pharmaceutical ingredients and medicinal products. (ICHQ8- Glossary at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002872.pdf)
Standard operating procedure	An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material but of a more general nature. (WHO guide to good manufacturing practice (GMP) requirements, at http://www.who.int/vaccines-documents/DocsPDF/www9651.pdf).
Stringent Regulatory Authority	A regulatory authority that is: A member of ICH prior to 23rd October 2015, namely the USFDA, the European Commission and the Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency, or An ICH observer prior to 23rd October 2015, namely the European Free Trade Association, as represented by Swissmedic and Health Canada, or A regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement prior to 23rd October 2015, namely Australia, Iceland, Liechtenstein and Norway.
Summary of Product Characteristics (SmPC)	Product information as approved by the Regulatory Authority. The SmPC serves as the basis for production of information for health personnel as well as for consumer information on labels and leaflets of medicinal products and for control of advertising. (WHO Medicines Regulatory Package. A Collection of Tools for Medicines Regulatory Authorities - Regulatory Support Series No. 014 at: http://infocollections.org/medregpack/interface/files/glossary.pdf)
Tentative Approval	If a generic drug product is ready for approval before the expiration of any patents or exclusivities accorded to the reference listed drug product, FDA issues a tentative approval letter to the applicant. The tentative approval letter details the circumstances associated with the tentative approval. FDA

	delays final approval of the generic drug product until all patent or exclusivity issues have been resolved. A tentative approval does not allow the applicant to market the generic drug product. (USFDA Glossary of terms, it can be found on line at Drugs@FDA Glossary of Terms).
Theoretical yield	The quantity that would be produced at any appropriate phase of manufacture, processing, or packaging of a particular drug product, based upon the quantity of components to be used, in the absence of any loss or an error in actual production. (WHO guide to good manufacturing practice (GMP) requirements, at http://www.who.int/vaccines-documents/DocsPDF/www9651.pdf).
Therapeutic Equivalence (TE)	Medicinal products are considered to be therapeutically equivalent only if they are pharmaceutical equivalents or pharmaceutical alternatives and their effect are essentially the same. This can be and have been scientifically demonstrated be bioequivalent. (Adapted from WHO glossary of terms)
Unique identifier	Is a unique code that is added to the medicinal product label (primary and/or secondary pack) in order to specifically identify and capture particulars of the product for market surveillance purposes. It may be in form of a code, barcode or security number that is unique for a specific product. The product registration number issued by PPB may be considered as a unique identifier.
Validation	Action of proving and documenting that any procedure, process, equipment, activity or system will, with a high degree of assurance, lead to the expected results. (Federation of Pharmaceutical Industries and Association; GMP for API manufacturer, at http://apic.cefic.org/pub/1gmp-api9604.pdf).
Variation	Variation is a change to a Marketing Authorization that is considered to fundamentally alter the terms of the MA for a medicinal product. (Glossary of terms and abbreviations/EMA it can be found at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/12/WC500099907.pdf).
Wholesale	All activities consisting of procuring, holding, supplying or exporting bulk medicinal products, apart from supplying medicinal products to the public. (PHIS Glossary 2009, can be found on line at: http://phis.goeg.at/index.aspx?alias=phisglossary).

PART V:

LIST OF STANDARD TERMS FOR PHARMACEUTICAL DOSAGE FORMS AND ROUTES OF ADMINISTRATION

1. INTRODUCTION AND GUIDANCE FOR USE

1.1 Scope

This list of standard terms for pharmaceutical dosage forms and routes of administration will assist in knowing all dosage forms used and routes used, accurate dose, protected dosage forms e.g. coated tablets, sealed ampoules, masked taste and odour, placement of drugs within body tissues, sustained release medication, controlled release medication, optimal drug action, insertion of drugs into body cavities (rectal, vaginal) and Use of desired vehicle for insoluble drugs. It has the double purpose to bring information to user (patient/prescriber) and distinguishing medicinal products having the same trade/generic name. Because of labelling purposes, it is imperative that any Standard Term and combination of Standard Terms is constructed with a view to the patient

However, information on the container and the route of administration need not always be included in the Standard Term but may appear elsewhere in the labelling, package leaflet and SmPC.

1.2 Guidance for use

The PPB List of Standard Terms covers dosage forms and routes of administration for the use in the marketing authorization application, Summary of Product Characteristics (SmPC), Patient Information leaflet and labelling of medicinal product for human use.

2. DEFINITIONS

For the purposes of the Standard Terms, the following definitions apply.

Pharmaceutical form

The pharmaceutical form may be:

a) a dosage form;

b) a combination of dosage forms; or

c) a combination of dosage form(s) and route(s)/method(s) of administration and/or container/administration device.

In the assessment of marketing authorization applications, pharmaceutical forms that differ only with respect to the containers/administration devices may not always be considered as different pharmaceutical forms.

Dosage form:

The dosage form is the physical manifestation of a medicinal product that contains the active ingredient(s) and/or excipient(s) that are intended to be delivered to the patient; it may refer to the form of presentation or the form of administration, which in some cases are identical.

a) Form of presentation:

The form of presentation is the dosage form of a medicinal product as manufactured and, where applicable, before reconstitution; where reconstitution is required before administration to the patient, the term includes the eventual form of administration.

Examples: Powder for solution for injection; Tablet

b) Form of administration

The form of administration is the dosage form of a medicinal product as administered to the patient, after any necessary reconstitution has been carried out.

Examples: Solution for injection; Tablet

Combined term

A combined term is a combination of existing Standard Terms or elements thereof that is constructed in order to properly characterize a medicinal product; a combined term may be a combination of dosage forms, or a combination of dosage form(s) and route(s)/method(s) of administration and/or container/administration device.

Examples: Powder and solution for solution for injection; Eye drops, solution in single-dose container.

Pharmaceutical forms

The list of Standard Terms does not distinguish between medicinal products as presented by the manufacturer (form of presentation) and medicinal products as administered to the patient (form of administration). However, for a term representing a form of presentation such as 'Powder for solution for injection', the words 'for solution for injection' indicate that a reconstitution is required, and that the resulting form of administration is 'solution for injection'.

The label of the medicinal product may be too small to permit the inclusion of the Standard Term(s). In addition to the Standard Terms given in the Dosage forms section, a number of patient-friendly terms (generally shortened versions of existing terms), which may be used for labelling only, in case of space limitation, are also proposed.

Where a term contains two or more dosage form elements, these elements are linked by 'and'; e.g. 'Powder and solvent for solution for injection'

If the same pharmaceutical form may be used in alternative ways, these ways are separated by '/', e.g. 'Gargle/mouthwash', 'Chewable/dispersible tablet'.

In the case of a powder that is dissolved in a small amount of solvent before it is diluted in a larger volume to be infused and this dilution is mandatory for safety reasons, the term 'concentrate' should appear in the pharmaceutical form (e.g. 'Powder for concentrate for solution for infusion'). If the powder that is dissolved in a small amount of solvent can either be administered as such or be further diluted before administration (i.e. no safety issue), there is no need to use the term 'concentrate' (e.g. 'Powder for solution for infusion').

The term 'modified-release' is not sufficiently precise for describing a particular product. A more specific term such as 'prolonged-release' or 'gastro-resistant' should be used, wherever applicable.

Routes of administration

The route of administration indicates the part of the body on which, through which or into which the medicinal product is to be introduced. The short terms proposed may be used for labelling only.

Where several routes of administration are intended for a medicinal product, the focus should be placed on the primary use for the creation of a standard term or a combination of standard terms, for example 'Oral use' is sufficient as the primary use for a request of 'Oral/gastric/gastroenteral use'.

3. PHARMACEUTICAL FORMS AND SHORT TERMS

Standard terms	**short terms**
BATH ADDITIVE	BATH ADDITIVE
BLADDER IRRIGATION	BLADDER IRRIGATION
BAR CHEWABLE	BAR CHEWABLE
BLOOD FRACTION MODIFIER	BLOOD FRACTION MODIFIER
BUCCAL FILM	BUCCAL FILM
BUCCAL TABLET	BUCCAL TABLET
CACHET	CACHET
CAPSULE	CAPSULE
CAPSULE, HARD SHELL	CAPSULE
CAPSULE, SOFT SHELL	CAPSULE
CHEWABLE CAPSULE, SOFT	CHEWABLE CAPSULE
CHEWABLE TABLET	CHEWABLE TABLET
COATED GRANULES IN SACHET	GRANULES
COATED TABLET	TABLET
COLLODION	COLLODION
COMPRESSED LOZENGE	LOZENGE
CONCENTRATE AND SOLVENT FOR CONCENTRATE FOR SOLUTION FOR INFUSION	CONCENTRATE AND SOLVENT FOR CONCENTRATE FOR SOLUTION FOR INFUSION
CONCENTRATE AND SOLVENT FOR CUTANEOUS SOLUTION	CONCENTRATE AND SOLVENT FOR CUTANEOUS SOLUTION
CONCENTRATE AND SOLVENT FOR SOLUTION FOR INFUSION	CONCENTRATE AND SOLVENT FOR SOLUTION FOR INFUSION
CONCENTRATE AND SOLVENT FOR SOLUTION FOR INJECTION	CONCENTRATE AND SOLVENT FOR SOLUTION FOR INJECTION
CONCENTRATE AND SOLVENT FOR SOLUTION FOR INJECTION/INFUSION	CONCENTRATE AND SOLVENT FOR SOLUTION FOR INJECTION/INFUSION
CONCENTRATE AND SOLVENT FOR SUSPENSION FOR INJECTION	CONCENTRATE AND SOLVENT FOR SUSPENSION FOR INJECTION
CONCENTRATE FOR CUTANEOUS SOLUTION	CONCENTRATE FOR CUTANEOUS SOLUTION
CONCENTRATE FOR CUTANEOUS SPRAY, EMULSION	CONCENTRATE FOR CUTANEOUS SPRAY, EMULSION
CONCENTRATE FOR DISPERSION FOR INFUSION	CONCENTRATE FOR DISPERSION FOR INFUSION
CONCENTRATE FOR EMULSION FOR INFUSION	CONCENTRATE FOR EMULSION FOR INFUSION
CONCENTRATE FOR GARGLE	CONCENTRATE FOR GARGLE
CONCENTRATE FOR HAEMODIALYSIS SOLUTION	CONCENTRATE FOR HAEMODIALYSIS SOLUTION
CONCENTRATE SOLUTION FOR INTRAVESICAL USE	CONCENTRATE SOLUTION FOR INTRAVESICAL USE
CONCENTRATE FOR ORAL SOLUTION	CONCENTRATE FOR ORAL SOLUTION
CONCENTRATE FOR ORAL SUSPENSION	CONCENTRATE FOR ORAL SUSPENSION

CONCENTRATE FOR ORAL/RECTAL SOLUTION	CONCENTRATE FOR ORAL/RECTAL SOLUTION
CONCENTRATE FOR RECTAL SOLUTION	CONCENTRATE FOR RECTAL SOLUTION
CONCENTRATE FOR SOLUTION FOR INFUSION	STERILE CONCENTRATE
CONCENTRATE FOR SOLUTION FOR INJECTION	STERILE CONCENTRATE
CONCENTRATE FOR SOLUTION FOR INJECTION/INFUSION	STERILE CONCENTRATE
CONCENTRATE FOR SOLUTION FOR PERITONEAL DIALYSIS	CONCENTRATE FOR SOLUTION FOR PERITONEAL DIALYSIS
CREAM	CREAM
CUTANEOUS EMULSION	CUTANEOUS LIQUID
CUTANEOUS FOAM	CUTANEOUS FOAM
CUTANEOUS PASTE	CUTANEOUS PASTE
CUTANEOUS PATCH	CUTANEOUS PATCH
CUTANEOUS POWDER	CUTANEOUS POWDER
CUTANEOUS SOLUTION	CUTANEOUS LIQUID
CUTANEOUS SPONGE	CUTANEOUS SPONGE
CUTANEOUS SOLUTION/CONCENTRATE FOR OROMUCOSAL SOLUTION	CUTANEOUS SOLUTION/CONCENTRATE FOR OROMUCOSAL SOLUTION
CUTANEOUS PATCH	CUTANEOUS PATCH
CUTANEOUS SPRAY	CUTANEOUS SPRAY
CUTANEOUS SPRAY, EMULSION	CUTANEOUS SPRAY
CUTANEOUS SPRAY, OINTMENT	CUTANEOUS SPRAY
CUTANEOUS SPRAY, POWDER	CUTANEOUS SPRAY
CUTANEOUS SPRAY, SOLUTION	CUTANEOUS SPRAY
CUTANEOUS SPRAY, SUSPENSION	CUTANEOUS SPRAY
CUTANEOUS STICK	CUTANEOUS STICK
CUTANEOUS SUSPENSION	CUTANEOUS LIQUID
CUTANEOUS OINTMENT	CUTANEOUS OINTMENT
DENTAL EMULSION	DENTAL LIQUID
DENTAL GEL	DENTAL GEL
DENTAL INSERT	DENTAL INSERT
DENTAL LIQUID	DENTAL LIQUID
DENTAL PASTE	DENTAL PASTE
DENTAL POWDER	DENTAL POWDER
DENTAL SOLUTION	DENTAL LIQUID
DENTAL STICK	DENTAL STICK
DENTAL SUSPENSION	DENTAL LIQUID
DENTURE LACQUER	DENTURE LACQUER
DISPERSIBLE TABLET	DISPERSIBLE TABLET
DISPERSION	DISPERSION
DISPERSION FOR INJECTION	DISPERSION FOR INJECTION
EAR CREAM	EAR CREAM
EAR DROPS	EAR DROPS
EAR DROPS, EMULSION	EAR DROPS
EAR DROPS, POWDER AND SOLVENT FOR SUSPENSION	EAR DROPS, POWDER AND SOLVENT FOR SUSPENSION
EAR DROPS, SOLUTION	EAR DROPS
EAR DROPS, SUSPENSION	EAR DROPS
EAR DROPS, SUSPENSION IN SINGLE-DOSE CONTAINER	EAR DROPS, SUSPENSION IN SINGLE-DOSE CONTAINER
EAR GEL	EAR GEL
EAR OINTMENT	EAR OINTMENT
EAR POWDER	EAR POWDER
EAR SPRAY, EMULSION	EAR SPRAY

EAR SPRAY, SOLUTION	EAR SPRAY
EAR SPRAY, SUSPENSION	EAR SPRAY
EAR STICK	EAR STICK
EAR TAMPON	EAR TAMPON
EAR WASH, EMULSION	EAR WASH
EAR WASH, SOLUTION	EAR WASH
EAR/EYE DROPS, SOLUTION	EAR/EYE DROPS, SOLUTION
EAR/EYE DROPS, SUSPENSION	EAR/EYE DROPS, SUSPENSION
EAR/EYE OINTMENT	EAR/EYE OINTMENT
EAR/EYE/NASAL DROPS, SOLUTION	EAR/EYE/NASAL DROPS, SOLUTION
EFFERVESCENT GRANULES	EFFERVESCENT GRANULES
EFFERVESCENT POWDER	EFFERVESCENT POWDER
EFFERVESCENT TABLET	EFFERVESCENT TABLET
EFFERVESCENT VAGINAL TABLET	EFFERVESCENT VAGINAL TABLET
EMULSION FOR INFUSION	INFUSION
EMULSION FOR INJECTION	INJECTION
EMULSION FOR INJECTION/INFUSION	INJECTION/INFUSION
ENDOCERVICAL GEL	ENDOCERVICAL GEL
ENDOSINUSIAL WASH, SUSPENSION	ENDOSINUSIAL WASH, SUSPENSION
ENDOTRACHEOPULMONARY INSTILLATION	ENDOTRACHEOPULMONARY INSTILLATION
ENDOTRACHEOPULMONARY INSTILLATION, POWDER AND SOLVENT FOR SOLUTION	ENDOTRACHEOPULMONARY INSTILLATION
ENDOTRACHEOPULMONARY INSTILLATION, POWDER FOR SOLUTION	ENDOTRACHEOPULMONARY INSTILLATION
ENDOTRACHEOPULMONARY INSTILLATION, SOLUTION	ENDOTRACHEOPULMONARY INSTILLATION
ENDOTRACHEOPULMONARY INSTILLATION, SUSPENSION	ENDOTRACHEOPULMONARY INSTILLATION
ENEMA	ENEMA
EYE CREAM	EYE CREAM
EYE DROPS	EYE DROPS
EYE DROPS, EMULSION	EYE DROPS, EMULSION
EYE DROPS, POWDER AND SOLVENT FOR SOLUTION	EYE DROPS, POWDER AND SOLVENT FOR SOLUTION
EYE DROPS, POWDER AND SOLVENT FOR SUSPENSION	EYE DROPS, POWDER AND SOLVENT FOR SUSPENSION
EYE DROPS, PROLONGED-RELEASE	EYE DROPS, PROLONGED-RELEASE
EYE DROPS, PROLONGED-RELEASE SOLUTION IN SINGLE-DOSE CONTAINER	EYE DROPS, PROLONGED-RELEASE SOLUTION IN SINGLE-DOSE CONTAINER
EYE DROPS, SOLUTION	EYE DROPS
EYE DROPS, SOLUTION IN SINGLE-DOSE CONTAINER	EYE DROPS, SOLUTION IN SINGLE-DOSE CONTAINER
EYE DROPS, SOLVENT FOR RECONSTITUTION	EYE DROPS, SOLVENT FOR RECONSTITUTION
EYE DROPS, SUSPENSION	EYE DROPS
EYE DROPS, SUSPENSION IN SINGLE-DOSE CONTAINER	EYE DROPS, SUSPENSION IN SINGLE-DOSE CONTAINER
EYE GEL	EYE GEL
EYE GEL IN SINGLE-DOSE CONTAINER	EYE GEL IN SINGLE-DOSE CONTAINER
EYE LOTION	EYE LOTION
EYE LOTION, SOLVENT FOR RECONSTITUTION	EYE LOTION, SOLVENT FOR RECONSTITUTION
EYE OINTMENT	EYE OINTMENT
EYE OINTMENT IN SINGLE-DOSE CONTAINER	EYE OINTMENT IN SINGLE-DOSE CONTAINER

FILM-COATED TABLET	TABLET
GARGLE	GARGLE
GARGLE, POWDER FOR SOLUTION	GARGLE, POWDER FOR SOLUTION
GARGLE, TABLET FOR SOLUTION	GARGLE, TABLET FOR SOLUTION
GARGLE/MOUTHWASH	GARGLE/MOUTHWASH
GARGLE/NASAL WASH	GARGLE/NASAL WASH
GAS AND SOLVENT FOR DISPERSION FOR INJECTION/INFUSION	GAS AND SOLVENT FOR DISPERSION FOR INJECTION/INFUSION
GASTROENTERAL EMULSION	GASTROENTERAL LIQUID
GASTROENTERAL LIQUID	GASTROENTERAL LIQUID
GASTROENTERAL SOLUTION	GASTROENTERAL LIQUID
GASTROENTERAL SUSPENSION	GASTROENTERAL LIQUID
GASTRO-RESISTANT CAPSULE	GASTRO-RESISTANT CAPSULE
GASTRO-RESISTANT CAPSULE, HARD	GASTRO-RESISTANT CAPSULE
GASTRO-RESISTANT CAPSULE, SOFT	GASTRO-RESISTANT CAPSULE
GASTRO-RESISTANT GRANULES	GASTRO-RESISTANT GRANULES
GASTRO-RESISTANT GRANULES FOR ORAL SUSPENSION	GASTRO-RESISTANT GRANULES FOR ORAL SUSPENSION
GASTRO-RESISTANT TABLET	GASTRO-RESISTANT TABLET
GEL	GEL
GINGIVAL GEL	GINGIVAL GEL
GINGIVAL PASTE	GINGIVAL PASTE
GINGIVAL SOLUTION	GINGIVAL SOLUTION
GRANULES	GRANULES
GRANULES AND SOLVENT FOR ORAL SUSPENSION	GRANULES AND SOLVENT FOR ORAL SUSPENSION
GRANULES AND SOLVENT FOR SUSPENSION FOR INJECTION	GRANULES AND SOLVENT FOR SUSPENSION FOR INJECTION
GRANULES FOR ORAL SOLUTION	GRANULES FOR ORAL SOLUTION
GRANULES FOR ORAL SUSPESION	GRANULES FOR ORAL SUSPESION
GRANULES FOR ORAL/RECTAL SUSPENSION	GRANULES FOR ORAL/RECTAL SUSPENSION
GRANULES FOR ORAL DROPS, SOLUTION	GRANULES FOR ORAL DROPS, SOLUTION
GRANULES FOR RECTAL SUSPENSION	GRANULES FOR RECTAL SUSPENSION
GRANULES FOR SYRUP	GRANULES FOR SYRUP
GRANULES FOR VAGINAL SOLUTION	GRANULES FOR VAGINAL SOLUTION
IMPLANT	IMPLANT
IMPLANT IN PRE-FILLED SYRINGE	IMPLANT IN PRE-FILLED SYRINGE
IMPLANTATION CHAIN	IMPLANTATION CHAIN
IMPLANTATION TABLET	IMPLANTATION TABLET
IMPREGNATED DRESSING	IMPREGNATED DRESSING
IMPREGNATED PAD	IMPREGNATED PAD
IMPREGNATED PLUG	IMPREGNATED PLUG
INFUSION	INFUSION
INHALATION GAS	INHALATION GAS
INHALATION POWDER	INHALATION POWDER
INHALATION POWDER, HARD CAPSULE	INHALATION POWDER
INHALATION POWDER, PRE-DISPENSED	INHALATION POWDER
INHALATION POWDER, TABLET	INHALATION POWDER
INHALATION SOLUTION	INHALATION SOLUTION
INHALATION VAPOUR	INHALATION VAPOUR
INHALATION VAPOUR, CAPSULE	INHALATION VAPOUR
INHALATION VAPOUR, EFFERVESCENT TABLET	INHALATION VAPOUR, EFFERVESCENT TABLET
INHALATION VAPOUR, EMULSION	INHALATION VAPOUR
INHALATION VAPOUR, IMPREGNATED PAD	INHALATION VAPOUR

INHALATION VAPOUR, LIQUID	INHALATION VAPOUR
INHALATION VAPOUR, OINTMENT	INHALATION VAPOUR
INHALATION VAPOUR, POWDER	INHALATION VAPOUR, POWDER
INHALATION VAPOUR, SOLUTION	INHALATION VAPOUR
INHALATION VAPOUR, TABLET	INHALATION VAPOUR
INJECTION	INJECTION
INTESTINAL GEL	INTESTINAL GEL
INTRAPERITONEAL SOLUTION	INTRAPERITONEAL SOLUTION
INTRAUTERINE DELIVERY SYSTEM	INTRAUTERINE DELIVERY SYSTEM
INTRAUTERINE FOAM	INTRAUTERINE FOAM
INTRAUTERINE LIQUID	INTRAUTERINE LIQUID
INTRAVESICAL SOLUTION	INTRAVESICAL SOLUTION
IRRIGATION SOLUTION	IRRIGATION SOLUTION
LOZENGE	LOZENGE
LIQUEFIED GAS FOR DENTAL USE	LIQUEFIED GAS FOR DENTAL USE
LYOPHILISATE FOR OCULONASAL SUSPENSION	LYOPHILISATE FOR OCULONASAL SUSPENSION
LYOPHILISATE FOR USE IN DRINKING WATER	LYOPHILISATE FOR USE IN DRINKING WATER
MEDICATED CHEWING-GUM	MEDICATED CHEWING-GUM
MEDICATED NAIL LACQUER	MEDICATED NAIL LACQUER
MEDICATED PLASTER	MEDICATED PLASTER
MEDICATED SPONGE	MEDICATED SPONGE
MEDICATED THREAD	MEDICATED THREAD
MEDICATED VAGINAL TAMPON	MEDICATED VAGINAL TAMPON
MEDICINAL GAS, COMPRESSED	MEDICINAL GAS, COMPRESSED
MEDICINAL GAS, CRYOGENIC	MEDICINAL GAS, CRYOGENIC
MEDICINAL GAS, LIQUEFIED	MEDICINAL GAS, LIQUEFIED
MODIFIED-RELEASE CAPSULE, HARD	MODIFIED-RELEASE CAPSULE, HARD
MODIFIED-RELEASE CAPSULE, SOFT	MODIFIED-RELEASE CAPSULE, SOFT
MODIFIED-RELEASE GRANULES	MODIFIED-RELEASE GRANULES
MODIFIED-RELEASE GRANULES FOR ORAL SUSPENSION	MODIFIED-RELEASE GRANULES FOR ORAL SUSPENSION
MODIFIED-RELEASE TABLET	MODIFIED-RELEASE TABLET
MOUTHWASH	MOUTHWASH
MOUTHWASH, POWDER FOR SOLUTION	MOUTHWASH, POWDER FOR SOLUTION
MOUTHWASH, TABLET FOR SOLUTION	MOUTHWASH, TABLET FOR SOLUTION
MUCO-ADHESIVE BUCCAL TABLET	MUCO-ADHESIVE BUCCAL TABLET
NASAL CREAM	NASAL CREAM
NASAL DROPS	NASAL DROPS
NASAL DROPS, EMULSION	NASAL DROPS
NASAL DROPS, SOLUTION	NASAL DROPS
NASAL DROPS, SOLUTION IN SINGLE-DOSE CONTAINER	NASAL DROPS, SOLUTION IN SINGLE-DOSE CONTAINER
NASAL DROPS, SUSPENSION	NASAL DROPS
NASAL GEL	NASAL GEL
NASAL OINTMENT	NASAL OINTMENT
NASAL POWDER	NASAL POWDER
NASAL SPRAY	NASAL SPRAY
NASAL SPRAY, EMULSION	NASAL SPRAY
NASAL SPRAY, POWDER FOR SOLUTION	NASAL POWDER
NASAL SPRAY, SOLUTION	NASAL SPRAY,
NASAL SPRAY, SOLUTION IN SINGLE-DOSE CONTAINER	NASAL SPRAY, SOLUTION IN SINGLE-DOSE CONTAINER
NASAL SPRAY, SOLUTION/OROMUCOSAL SOLUTION	NASAL SPRAY, SOLUTION/OROMUCOSAL SOLUTION
NASAL SPRAY, SUSPENSION	NASAL SPRAY, SUSPENSION

NASAL STICK	NASAL STICK
NASAL WASH	NASAL WASH
NASAL/OROMUCOSAL SOLUTION	NASAL/OROMUCOSAL SOLUTION
NASAL/OROMUCOSAL SPRAY, SOLUTION	NASAL/OROMUCOSAL SPRAY, SOLUTION
NEBULISER EMULSION	NEBULISER LIQUID
NEBULISER LIQUID	NEBULISER LIQUID
NEBULISER SOLUTION	NEBULISER LIQUID
NEBULISER SUSPENSION	NEBULISER LIQUID
OINTMENT	OINTMENT
OPHTHALMIC INSERT	OPHTHALMIC INSERT
OPHTHALMIC STRIP	OPHTHALMIC STRIP
ORAL DROPS	ORAL DROPS
ORAL DROPS, EMULSION	ORAL DROPS
ORAL DROPS, GRANULES FOR SOLUTION	ORAL DROPS, GRANULES FOR SOLUTION
ORAL DROPS, LIQUID	ORAL DROPS
ORAL DROPS, POWDER FOR SUSPENSION	ORAL DROPS, POWDER FOR SUSPENSION
ORAL DROPS, SOLUTION	ORAL DROPS
ORAL DROPS, SUSPENSION	ORAL DROPS
ORAL EMULSION	ORAL LIQUID
ORAL GEL	ORAL GEL
ORAL GUM	ORAL GUM
ORAL LIQUID	ORAL LIQUID
ORAL LYOPHILISATE	ORAL LYOPHILISATE
ORAL PASTE	ORAL PASTE
ORAL POWDER	ORAL POWDER
ORAL SOLUTION	ORAL LIQUID
ORAL SOLUTION IN SINGLE-DOSE CONTAINER	ORAL SOLUTION IN SINGLE-DOSE CONTAINER
ORAL SOLUTION/CONCENTRATE FOR NEBULISER SOLUTION	ORAL SOLUTION/CONCENTRATE FOR NEBULISER SOLUTION
ORAL SUSPENSION	ORAL LIQUID
ORAL/RECTAL SOLUTION	ORAL/RECTAL LIQUID
ORAL/RECTAL SUSPENSION	ORAL/RECTAL LIQUID
ORODISPERSIBLE FILM	ORODISPERSIBLE FILM
ORODISPERSIBLE TABLET	ORODISPERSIBLE TABLET
OROMUCOSAL CAPSULE	OROMUCOSAL CAPSULE
OROMUCOSAL CREAM	OROMUCOSAL CREAM
OROMUCOSAL DROPS	OROMUCOSAL DROPS
OROMUCOSAL GEL	OROMUCOSAL GEL
OROMUCOSAL LIQUID	OROMUCOSAL LIQUID
OROMUCOSAL OINTMENT	OROMUCOSAL OINTMENT
OROMUCOSAL PASTE	OROMUCOSAL PASTE
OROMUCOSAL PATCH	OROMUCOSAL PATCH
OROMUCOSAL POWDER IN POUCH	OROMUCOSAL POWDER IN POUCH
OROMUCOSAL SOLUTION	OROMUCOSAL LIQUID
OROMUCOSAL SPRAY, EMULSION	OROMUCOSAL SPRAY
OROMUCOSAL SPRAY, SOLUTION	OROMUCOSAL SPRAY
OROMUCOSAL SPRAY, SUSPENSION	OROMUCOSAL SPRAY
OROMUCOSAL SUSPENSION	OROMUCOSAL LIQUID
OROMUCOSAL/LARYNGOPHARYNGEAL SOLUTION	OROMUCOSAL/LARYNGOPHARYNGEAL SOLUTION
PASTILLE	PASTILLE
PERIODONTAL GEL	PERIODONTAL GEL
PERIODONTAL INSERT	PERIODONTAL INSERT
PERIODONTAL POWDER	PERIODONTAL POWDER
PESSARY	PESSARY

PILLULES	PILLULES
PILLULES IN SINGLE-DOSE CONTAINER	PILLULES IN SINGLE-DOSE CONTAINER
PLASTER FOR PROVOCATION TEST	PLASTER FOR PROVOCATION TEST
POUCH	POUCH
POULTICE	POULTICE
POWDER AND SOLVENT FOR SOLUTION FOR INJECTION	POWDER AND SOLVENT FOR SOLUTION FOR INJECTION
POWDER AND SOLVENT FOR CONCENTRATE FOR SOLUTION FOR INFUSION	POWDER AND SOLVENT FOR CONCENTRATE FOR SOLUTION FOR INFUSION
POWDER AND SOLVENT FOR CUTANEOUS SOLUTION	POWDER AND SOLVENT FOR CUTANEOUS SOLUTION
POWDER AND SOLVENT FOR DISPERSION FOR INJECTION	POWDER AND SOLVENT FOR DISPERSION FOR INJECTION
POWDER AND SOLVENT FOR EMULSION FOR INJECTION	POWDER AND SOLVENT FOR EMULSION FOR INJECTION
POWDER AND SOLVENT FOR ENDOCERVICAL GEL	POWDER AND SOLVENT FOR ENDOCERVICAL GEL
POWDER AND SOLVENT FOR ENDOSINUSIAL SOLUTION	POWDER AND SOLVENT FOR ENDOSINUSIAL SOLUTION
POWDER AND SOLVENT FOR EPILESIONAL SOLUTION	POWDER AND SOLVENT FOR EPILESIONAL SOLUTION
POWDER AND SOLVENT FOR GINGIVAL GEL	POWDER AND SOLVENT FOR GINGIVAL GEL
POWDER AND SOLVENT FOR IMPLANTATION PASTE	POWDER AND SOLVENT FOR IMPLANTATION PASTE
POWDER AND SOLVENT FOR INSTILLATION SOLUTION FOR INTRAOCULAR USE	POWDER AND SOLVENT FOR INSTILLATION SOLUTION FOR INTRAOCULAR USE
POWDER AND SOLVENT FOR INTRAVESICAL SOLUTION	POWDER AND SOLVENT FOR INTRAVESICAL SOLUTION
POWDER AND SOLVENT FOR INTRAVESICAL SUSPENSION	POWDER AND SOLVENT FOR INTRAVESICAL SUSPENSION
POWDER AND SOLVENT FOR NEBULISER SOLUTION	POWDER AND SOLVENT FOR NEBULISER SOLUTION
POWDER AND SOLVENT FOR ORAL SOLUTION	POWDER AND SOLVENT FOR ORAL SOLUTION
POWDER AND SOLVENT FOR ORAL SUSPENSION	POWDER AND SOLVENT FOR ORAL SUSPENSION
POWDER AND SOLVENT FOR PROLONGED-RELEASE SUSPENSION FOR INJECTION	POWDER AND SOLVENT FOR PROLONGED-RELEASE SUSPENSION FOR INJECTION
POWDER AND SOLVENT FOR SEALANT	POWDER AND SOLVENT FOR SEALANT
POWDER AND SOLVENT FOR SOLUTION FOR INFUSION	POWDER AND SOLVENT FOR SOLUTION FOR INFUSION
POWDER AND SOLVENT FOR SOLUTION FOR INJECTION	POWDER AND SOLVENT FOR SOLUTION FOR INJECTION
POWDER AND SOLVENT FOR SOLUTION FOR INJECTION IN CARTRIDGE	POWDER AND SOLVENT FOR SOLUTION FOR INJECTION IN CARTRIDGE
POWDER AND SOLVENT FOR SOLUTION FOR INJECTION IN PRE-FILLED PEN	POWDER AND SOLVENT FOR SOLUTION FOR INJECTION IN PRE-FILLED PEN
POWDER AND SOLVENT FOR SOLUTION FOR INJECTION IN PRE-FILLED SYRINGE	POWDER AND SOLVENT FOR SOLUTION FOR INJECTION IN PRE-FILLED SYRINGE
POWDER AND SOLVENT FOR SOLUTION FOR INJECTION/ SKIN-PRICK TEST	POWDER AND SOLVENT FOR SOLUTION FOR INJECTION/ SKIN-PRICK TEST
POWDER AND SOLVENT FOR SOLUTION FOR INJECTION/INFUSION	POWDER AND SOLVENT FOR SOLUTION FOR INJECTION/INFUSION

POWDER AND SOLVENT FOR SUSPENSION FOR INJECTION	POWDER AND SOLVENT FOR SUSPENSION FOR INJECTION
POWDER AND SOLVENT FOR SUSPENSION FOR INJECTION IN PRE-FILLED SYRINGE	POWDER AND SOLVENT FOR SUSPENSION FOR INJECTION IN PRE-FILLED SYRINGE
POWDER AND SUSPENSION FOR SUSPENSION FOR INJECTION	POWDER AND SUSPENSION FOR SUSPENSION FOR INJECTION
POWDER FOR BLADDER IRRIGATION	POWDER FOR BLADDER IRRIGATION
POWDER FOR CONCENTRATE FOR DISPERSION FOR INFUSION	POWDER FOR CONCENTRATE FOR DISPERSION FOR INFUSION
POWDER FOR CONCENTRATE FOR INTRAVESICAL SUSPENSION	POWDER FOR CONCENTRATE FOR INTRAVESICAL SUSPENSION
POWDER FOR CONCENTRATE FOR SOLUTION FOR HAEMODIALYSIS	POWDER FOR CONCENTRATE FOR SOLUTION FOR HAEMODIALYSIS
POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION	POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION
POWDER FOR CONCENTRATE FOR SOLUTION FOR INJECTION/INFUSION	POWDER FOR CONCENTRATE FOR SOLUTION FOR INJECTION/INFUSION
POWDER FOR CUTANEOUS SOLUTION	POWDER FOR CUTANEOUS SOLUTION
POWDER FOR DENTAL SOLUTION	POWDER FOR DENTAL SOLUTION
POWDER FOR DISPERSION FOR INFUSION	POWDER FOR DISPERSION FOR INFUSION
POWDER FOR EPILESIONAL SOLUTION	POWDER FOR EPILESIONAL SOLUTION
POWDER FOR IMPLANTATION SUSPENSION	POWDER FOR IMPLANTATION SUSPENSION
POWDER FOR INFUSION	POWDER FOR INFUSION
POWDER FOR INJECTION	POWDER FOR INJECTION
POWDER FOR INTRAVESICAL SOLUTION	POWDER FOR INTRAVESICAL SOLUTION
POWDER FOR INTRAVESICAL SOLUTION/SOLUTION FOR INJECTION	POWDER FOR INTRAVESICAL SOLUTION/SOLUTION FOR INJECTION
POWDER FOR INTRAVESICAL SUSPENSION	POWDER FOR INTRAVESICAL SUSPENSION
POWDER FOR NEBULISER SOLUTION	POWDER FOR NEBULISER SOLUTION
POWDER FOR NEBULISER SUSPENSION	POWDER FOR NEBULISER SUSPENSION
POWDER FOR ORAL SOLUTION	POWDER FOR ORAL SOLUTION
POWDER FOR ORAL SUSPENSION	POWDER FOR ORAL SUSPENSION
POWDER FOR ORAL/RECTAL SUSPENSION	POWDER FOR ORAL/RECTAL SUSPENSION
POWDER FOR RECTAL SOLUTION	POWDER FOR RECTAL SOLUTION
POWDER FOR RECTAL SUSPENSION	POWDER FOR RECTAL SUSPENSION
POWDER FOR SOLUTION FOR INFUSION	POWDER FOR SOLUTION FOR INFUSION
POWDER FOR SOLUTION FOR INJECTION	POWDER FOR SOLUTION FOR INJECTION
POWDER FOR SOLUTION FOR INJECTION/INFUSION	POWDER FOR SOLUTION FOR INJECTION/INFUSION
POWDER FOR SOLUTION FOR INTRAOCULAR IRRIGATION	POWDER FOR SOLUTION FOR INTRAOCULAR IRRIGATION
POWDER FOR SOLUTION FOR IONTOPHORESIS	POWDER FOR SOLUTION FOR IONTOPHORESIS
POWDER FOR SUSPENSION FOR INJECTION	POWDER FOR SUSPENSION FOR INJECTION
POWDER FOR SYRUP	POWDER FOR SYRUP
POWDER, DISPERSION AND SOLVENT FOR CONCENTRATE FOR DISPERSION FOR INFUSION	POWDER, DISPERSION AND SOLVENT FOR CONCENTRATE FOR DISPERSION FOR INFUSION
PRESSURISED INHALATION	PRESSURISED INHALATION
PRESSURISED INHALATION, EMULSION	PRESSURISED INHALATION, EMULSION
PRESSURISED INHALATION, SOLUTION	PRESSURISED INHALATION, SOLUTION

PRESSURISED INHALATION, SUSPENSION	PRESSURISED INHALATION, SUSPENSION
PROLONGED-RELEASE CAPSULE	PROLONGED-RELEASE CAPSULE
PROLONGED-RELEASE CAPSULE, HARD	PROLONGED-RELEASE CAPSULE
PROLONGED-RELEASE CAPSULE, SOFT	PROLONGED-RELEASE CAPSULE
PROLONGED-RELEASE GRANULES	PROLONGED-RELEASE GRANULES
PROLONGED-RELEASE GRANULES FOR ORAL SUSPENSION	PROLONGED-RELEASE GRANULES FOR ORAL SUSPENSION
PROLONGED-RELEASE SUSPENSION FOR INJECTION	PROLONGED-RELEASE SUSPENSION FOR INJECTION
PROLONGED-RELEASE SUSPENSION FOR INJECTION IN PRE-FILLED SYRINGE	PROLONGED-RELEASE SUSPENSION FOR INJECTION IN PRE-FILLED SYRINGE
PROLONGED-RELEASE TABLET	PROLONGED-RELEASE TABLET
RADIONUCLIDE GENERATOR	RADIONUCLIDE GENERATOR
RADIOPHARMACEUTICAL PRECURSOR	RADIOPHARMACEUTICAL PRECURSOR
RADIOPHARMACEUTICAL PRECURSOR, SOLUTION	RADIOPHARMACEUTICAL PRECURSOR, SOLUTION
RECTAL CAPSULE	RECTAL CAPSULE
RECTAL CREAM	RECTAL CREAM
RECTAL EMULSION	RECTAL EMULSION
RECTAL FOAM	RECTAL FOAM
RECTAL GEL	RECTAL GEL
RECTAL OINTMENT	RECTAL OINTMENT
RECTAL SOLUTION	ENEMA
RECTAL SUSPENSION	ENEMA
RECTAL TAMPON	RECTAL TAMPON
SEALANT	SEALANT
SHAMPOO	SHAMPOO
SOLUBLE TABLET	SOLUBLE TABLET
SOLUTION AND SUSPENSION FOR SUSPENSION FOR INJECTION IN PRE-FILLED SYRINGE	SOLUTION AND SUSPENSION FOR SUSPENSION FOR INJECTION IN PRE-FILLED SYRINGE
SOLUTION FOR BLOOD FRACTION MODIFICATION	SOLUTION FOR BLOOD FRACTION MODIFICATION
SOLUTION FOR CARDIOPLEGIA	SOLUTION FOR CARDIOPLEGIA
SOLUTION FOR HAEMODIAFILTRATION	SOLUTION FOR HAEMODIAFILTRATION
SOLUTION FOR HAEMODIALYSIS	SOLUTION FOR HAEMODIALYSIS
SOLUTION FOR HAEMODIALYSIS/HAEMOFILTRATION	SOLUTION FOR HAEMODIALYSIS/HAEMOFILTRATION
SOLUTION FOR HAEMOFILTRATION	SOLUTION FOR HAEMOFILTRATION
SOLUTION FOR INFUSION	INTRAVENOUS INFUSION
SOLUTION FOR INFUSION IN ADMINISTRATION SYSTEM	SOLUTION FOR INFUSION IN ADMINISTRATION SYSTEM
SOLUTION FOR INFUSION IN PRE-FILLED SYRINGE	SOLUTION FOR INFUSION IN PRE-FILLED SYRINGE
SOLUTION FOR INJECTION	INJECTION
SOLUTION FOR INJECTION IN CARTRIDGE	SOLUTION FOR INJECTION IN CARTRIDGE
SOLUTION FOR INJECTION IN NEEDLE-FREE INJECTOR	SOLUTION FOR INJECTION IN NEEDLE-FREE INJECTOR
SOLUTION FOR INJECTION IN PRE-FILLED PEN	SOLUTION FOR INJECTION IN PRE-FILLED PEN
SOLUTION FOR INJECTION IN PRE-FILLED SYRINGE	SOLUTION FOR INJECTION IN PRE-FILLED SYRINGE
SOLUTION FOR INJECTION/INFUSION	SOLUTION FOR INJECTION/INFUSION
SOLUTION FOR INJECTION, LYOPHILISATE	SOLUTION FOR INJECTION, LYOPHILISATE

SOLUTION FOR INFUSION, LYOPHILISATE	SOLUTION FOR INFUSION, LYOPHILISATE
SOLUTION FOR INJECTION/INFUSION IN PRE-FILLED SYRINGE	SOLUTION FOR INJECTION/INFUSION IN PRE-FILLED SYRINGE
SOLUTION FOR IONTOPHORESIS	SOLUTION FOR IONTOPHORESIS
SOLUTION FOR ORGAN PRESERVATION	SOLUTION FOR ORGAN PRESERVATION
SOLUTION FOR PERITONEAL DIALYSIS	SOLUTION FOR PERITONEAL DIALYSIS
SOLUTION FOR PROVOCATION TEST	SOLUTION FOR PROVOCATION TEST
SOLUTION FOR SEALANT	SOLUTION FOR SEALANT
SOLUTION FOR SKIN-PRICK TEST	SOLUTION FOR SKIN-PRICK TEST
SOLUTION FOR SKIN-SCRATCH TEST	SOLUTION FOR SKIN-SCRATCH TEST
SOLVENT FOR PARENTERAL USE	SOLVENT FOR PARENTERAL USE
SOLVENT FOR SOLUTION FOR INFUSION	SOLVENT FOR SOLUTION FOR INFUSION
SOLVENT FOR SOLUTION FOR INTRAOCULAR IRRIGATION	SOLVENT FOR SOLUTION FOR INTRAOCULAR IRRIGATION
STERILE CONCENTRATE	STERILE CONCENTRATE
STOMACH IRRIGATION	STOMACH IRRIGATION
SUBLINGUAL FILM	SUBLINGUAL FILM
SUBLINGUAL SPRAY, EMULSION	SUBLINGUAL SPRAY
SUBLINGUAL SPRAY, SOLUTION	SUBLINGUAL SPRAY
SUBLINGUAL SPRAY, SUSPENSION	SUBLINGUAL SPRAY
SUBLINGUAL TABLET	SUBLINGUAL TABLET
SUPPOSITORY	SUPPOSITORY
SUSPENSION AND EFFERVESCENT GRANULES FOR ORAL SUSPENSION	SUSPENSION AND EFFERVESCENT GRANULES FOR ORAL SUSPENSION
SUSPENSION AND SOLUTION FOR SPRAY	SUSPENSION AND SOLUTION FOR SPRAY
SUSPENSION AND SOLVENT FOR SUSPENSION FOR INJECTION	SUSPENSION AND SOLVENT FOR SUSPENSION FOR INJECTION
SUSPENSION FOR INFUSION	SUSPENSION FOR INFUSION
SUSPENSION FOR INJECTION IN CARTRIDGE	SUSPENSION FOR INJECTION IN CARTRIDGE
SUSPENSION FOR INJECTION IN PRE-FILLED PEN	SUSPENSION FOR INJECTION IN PRE-FILLED PEN
SUSPENSION FOR INJECTION IN PRE-FILLED SYRINGE	SUSPENSION FOR INJECTION IN PRE-FILLED SYRINGE
SUSPENSION FOR INJECTION, LYOPHILISATE	SUSPENSION FOR INJECTION, LYOPHILISATE
SYRUP	SYRUP
TABLET	TABLET
TABLET AND POWDER FOR ORAL SOLUTION	TABLET AND POWDER FOR ORAL SOLUTION
TABLET AND SOLVENT FOR RECTAL SUSPENSION	TABLET AND SOLVENT FOR RECTAL SUSPENSION
TABLET FOR RECTAL SOLUTION	TABLET FOR RECTAL SOLUTION
TABLET FOR ORAL SUSPENSION	TABLET FOR ORAL SUSPENSION
TABLET FOR VAGINAL SOLUTION	TABLET FOR VAGINAL SOLUTION
TOOTHPASTE	TOOTHPASTE
TRANSDERMAL GEL	TRANSDERMAL GEL
TRANSDERMAL PATCH	TRANSDERMAL PATCH
TRANSDERMAL SOLUTION	TRANSDERMAL SOLUTION
TRANSDERMAL SPRAY, SOLUTION	TRANSDERMAL SPRAY
TRANSDERMAL PATCH	TRANSDERMAL PATCH
URETHRAL GEL	URETHRAL GEL
URETHRAL STICK	URETHRAL STICK
VAGINAL CAPSULE	VAGINAL CAPSULE
VAGINAL CAPSULE, HARD	VAGINAL CAPSULE
VAGINAL CAPSULE, SOFT	VAGINAL CAPSULE
VAGINAL CREAM	VAGINAL CREAM

VAGINAL DELIVERY SYSTEM	VAGINAL DELIVERY SYSTEM
VAGINAL EMULSION	VAGINAL LIQUID
VAGINAL FOAM	VAGINAL FOAM
VAGINAL GEL	VAGINAL GEL
VAGINAL OINTMENT	VAGINAL OINTMENT
VAGINAL SOLUTION	VAGINAL LIQUID
VAGINAL SUSPENSION	VAGINAL LIQUID
VAGINAL TABLET	VAGINAL TABLET
WOUND STICK	WOUND STICK

4. ROUTES OF ADMINISTRATION

NAMES	**SHORT TERM**
AURICULAR	OTIC
BUCCAL	BUCCAL
CONJUNCTIVAL	CONJUNC
CUTANEOUS	CUTAN
DENTAL	DENTAL
ENDOCERVICAL	E-CERVIC
ENDOSINUSIAL	E-SINUS
ENDOTRACHEAL	E-TRACHE
ENDOTRACHEOPULMONARY	
EPIDURAL	EPIDUR
EPILESIONAL	EPILESIONAL
EXTRA-AMNIOTIC	X-AMNI
EXTRACORPOREAL	X-CORPOR
GASTRIC	
GASTROENTERAL	
GINGIVAL	
HEMODIALYSIS	HEMO
IMPLANT	
INFILTRATION	INFIL
INHALATIONAL	
INTERSTITIAL	INTERSTIT
INTRA-ABDOMINAL	I-ABDOM
INTRA-AMNIOTIC	I-AMNI
INTRA-ARTERIAL	I-ARTER
INTRA-ARTICULAR	I-ARTIC
INTRABILIARY	I-BILI
INTRABRONCHIAL	I-BRONCHI
INTRABURSAL	I-BURSAL

INTRACAMERAL	
INTRACARDIAC	I-CARDI
INTRACARTILAGINOUS	I-CARTIL
INTRACAUDAL	I-CAUDAL
INTRACAVERNOUS	I-CAVERN
INTRACAVITARY	I-CAVIT
INTRACEREBRAL	I-CERE
INTRACERVICAL	
INTRACISTERNAL	I-CISTERN
INTRACORNEAL	I-CORNE
INTRACORONARY	I-CORONARY
INTRACORPUS CAVERNOSUM	I-CORPOR
INTRADERMAL	I-DERMAL
INTRADISCAL	I-DISCAL
INTRADUCTAL	I-DUCTAL
INTRADUODENAL	I-DUOD
INTRADURAL	I-DURAL
INTRA-EPIDERMAL	I-EPIDERM
INTRA-ESOPHAGEAL	I-ESO
INTRAHEPATIC	
INTRALESIONAL	I-LESION
INTRALYMPHATIC	I-LYMPHAT
INTRAMEDULLARY	I-MEDUL
INTRAMENINGEAL	I-MENIN
INTRAMUSCULAR	IM
INTRAOCULAR	I-OCUL
INTRAOSSEOUS	
INTRAOVARIAN	I-OVAR
INTRAPERICARDIAL	I-PERICARD
INTRAPERITONEAL	I-PERITON
INTRAPLEURAL	I-PLEURAL
INTRAPROSTATIC	I-PROSTAT
INTRAPULMONARY	I-PULMON
INTRASINAL	I-SINAL
INTRASYNOVIAL	I-SYNOV
INTRASTERNAL	
INTRATHECAL	IT
INTRATUMORAL	I-TUMOR

INTRAUTERINE	I-UTER
INTRAVENOUS	IV
INTRAVENOUS DRIP	IV DRIP
INTRAVENOUS BOLUS	IV BOLUS
INTRAVASCULAR	I-VASC
INTRAVITREAL	I-VITRE
IN VITRO	
IONTOPHORESIS	ION
LARYNGOPHARYNGEAL	LARYN
NASAL	NASAL
NASOGASTRIC	NG
OCCLUSIVE DRESSING TECHNIQUE	OCCLUS
OPHTHALMIC	OPHTHALM
ORAL	ORAL
OROMUCOSAL	
OROPHARYNGEAL	ORO
OTHER	OTHER
PARENTERAL	PAREN
PERIARTICULAR	P-ARTIC
PERICUTANEOUS	PERCUT
PERINEURAL	P-NEURAL
PERIODONTAL	P-ODONT
PERIOSSEOUS	
RECTAL	RECTAL
RETROBULBAR	RETRO
ROUTE OF ADMINISTRATION NOT APPLICABLE	NA
SUBCONJUNCTIVAL	S-CONJUNC
SUBCUTANEOUS	SC
SUBLINGUAL	SL
SUBMUCOSAL	S-MUCOS
TOPICAL	TOPIC
TRANSDERMAL	T-DERMAL
TRANSPLACENTAL	T-PLACENT
URETERAL	URETER
URETHRAL	URETH
VAGINAL	VAGIN

5. REFERENCES

1. Routes of Administration ICH M5 Controlled Vocabulary, CHMP/ICH/175860/2005, May 2005
2. XEVMPD Routes of Administration, Standard Term List, EMA/136146/2012, February 2012
3. XEVMPD Pharmaceutical Dose Forms, Standard Term List, EMA/136157/2012, Rev.6, February 2012
4. Pharmaceutical dosage forms, USP29

PART VI:

GUIDELINES ON REGISTRATION OF FIXED DOSE COMBINATION PHARMACEUTICAL PRODUCTS

ABBREVIATIONS

API	Active pharmaceutical ingredient
BCS	Biopharmaceutics Classification Scheme
BCS #1	Biopharmaceutics class number 1 (the most favourable)
CHMP	Committee for Medicinal Products for Human Use; *see also*
CPMP	Committee for Medicinal Products for Human Use (CHMP), formerly the Committee for Proprietary Medicinal Products
CPP	Certificate of pharmaceutical product
EMEA	European Medicines Agency, formerly the European Medicines Evaluation Agency
EU	European Union
FDA	Food and Drug Administration of the USA
FDC	Fixed-dose combination (*see* Glossary)
FDC-FPP	Fixed-dose combination finished pharmaceutical product
FPP	Finished Pharmaceutical Product
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GSP	Good Storage Practice
GTDP	Good Trade and Distribution Practice
ICH	International Conference on Harmonization
IUTLD	International Union of Tuberculosis and Lung Disease
MIC	Minimum Inhibitory Concentration
PP	Per-Protocol (a form of clinical trial design and analysis)
PPB	Pharmacy and Poisons Board
SPC	Summary of Product Characteristics (*see* Glossary)
WHO	World Health Organization

1. SCOPE

1.1 The scope of these guidelines covers prescription and non-prescription medicines.

1.2 Similar principles and guidance provided in this document should apply to the registration of prescription and non-prescription products. Nevertheless, the risk–benefit considerations (and consequently data requirements) may be different.

1.3 FDCs are getting highly popular in the pharmaceutical markets of developing countries and have been particularly flourishing in the last few years. Unfortunately, scientific literature has provided evidence that many FDCs being introduced in certain countries are irrational. Regulatory authorities should take due care in implementing this guidance and can also take guidance of the World Health Organization's (WHO) Model List of Essential Medicines, which provides examples of some rational FDCs.

1.4 The principles in these guidelines shall also apply to chemical combinations and complexes that comprise more than one active.

1.5 The scientific principles applicable to FDC products will also be applied in the assessment of co-packaged medicines.

2. GENERAL CONSIDERATIONS

2.1 These guidelines are intended to be used in conjunction with the PPB guidelines on submission of documentation for registration of human medicinal products.

2.2 Appendices 2, 3 and 4 provide guidance on subjects that are not exclusive to FDCs, but are nevertheless important in this context, and for which suitable guidance is not otherwise readily available.

2.3 It is important that access to useful, new FDCs should not be delayed by unnecessary constraints. These guidelines are not intended to define the only means of demonstrating the advantages and disadvantages of a new FDC. In some cases an alternative approach may be appropriate, for example when:

2.3.1 Scientific developments allow alternative means of achieving the same goals.

2.3.2 A circumstance unique to the product in question can be demonstrated.

2.3.3 An original but acceptable approach is devised.

2.3.4 Sufficient alternative studies have been conducted which, although not exactly what the guidelines seek, nevertheless satisfy the criteria of quality, safety and efficacy. When these guidelines (or others referred to herein) describe evidence that is required, applicants may either: provide the requested evidence, or provide an alternative form of evidence that addresses the same issues. In this case, the application should include an explanation and justification of the approach taken.

2.4 It is not always necessary to generate new (original) data. Evidence may be obtained from the scientific literature, subject to its being of adequate quality (see Appendix 2 entitled *Principles for determining whether data from the scientific literature are acceptable*).

An application for a marketing authorization may comprise:

2.4.1 Entirely original data.

2.4.2 Entirely data from the literature.

2.4.3 Both original data and data from the literature (a "generic" submission). For FDC-FPPs, it is likely that generic submissions will be the most common type.

The scientific literature rarely contains enough adequately validated information on quality to allow the full quality data set to be based solely on data from the literature. In particular, the complete formulation and method of manufacture are rarely specified. Consequently, the quality data set is almost always either totally original or generic.

2.5 When these guidelines request that an applicant explain and/or justify non-conformity with requirements, a suitable argument should be included in the section that discusses the advantages and

disadvantages of the combination (see below), together with cross-references to data elsewhere in the submission.

2.6 When an applicant is unsure of registration requirements or wishes to deviate from these guidelines, prior consultation with the relevant regulatory authority may be advantageous. However, applicants should not request advice until they have read all relevant guidelines and WHO's *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for a drug regulatory authority* (1999) or updates thereof. Not all of the guidelines in Tables 1–5 are necessarily relevant to a particular enquiry; the particulars of each case should be considered.

2.7 Risk–benefit assessments for FDCs should take into consideration any differences in anticipated patient populations. Consequently, decisions on the same data set may vary between different national drug regulatory authorities.

3. DEFINITIONS

The definitions given below apply solely to the terms as used in these guidelines. They may have different meanings in other contexts.

Active pharmaceutical ingredient (API)

Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form. When so used the API becomes the active moiety as defined below, often termed simply the active. The API may be a salt, hydrate or other form of the active moiety, or may be the active moiety itself. Active moieties are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

Active moiety

The term used for the therapeutically active entity in the final formulation of therapeutic goods, irrespective of the form of the API. The active is alternative

terminology with the same meaning. For example, if the API is propranolol hydrochloride, the active moiety (the active) is propranolol.

Applicant

The person or company who submits an application for marketing authorization of a new pharmaceutical product, an update to an existing marketing authorization or a variation to an existing market authorization.

Certificate of pharmaceutical product

A WHO-type certificate of the form described in Guidelines for implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce. Geneva, World Health Organization, 1998.

Comparator

The finished pharmaceutical product with which an FDC-FPP is to be compared. The comparison may be by means of bioequivalence studies or clinical studies of safety and/or effectiveness. A single study may use more than one comparator, for example several single entity FPPs. A comparator may be a placebo.

Co-packaged product

A product consisting of two or more separate pharmaceutical products in their final dosage forms that are packaged together for distribution to patients in the co-packaging.

Drug

Any substance or product for human or veterinary use that is intended to modify or explore physiological states for the benefit of the recipient.

Finished pharmaceutical product (FPP)

A product that has undergone all stages of production, including packaging in its final container and labelling. An FPP may contain one or more active

Fixed-dose combination (FDC)

A combination of two or more actives in a fixed ratio of doses. This term is used generically to mean a particular combination of actives irrespective of

the formulation or brand. It may be administered as single entity products given concurrently or as a finished pharmaceutical product.

Fixed-dose combination finished pharmaceutical product (FDC-FPP)

A finished pharmaceutical product that contains two or more actives.

Generic products

The term generic product has somewhat different meanings in different jurisdictions. Use of this term has therefore been avoided as far as possible, and the term multisource pharmaceutical product is used instead (see the definition below). Multisource products may be marketed either under the approved non-proprietary name or under a brand (proprietary) name. They may be marketed in dosage forms and/or strengths different to those of the innovator products.

Where the term generic product is used, it means a pharmaceutical product, usually intended to be interchangeable with the innovator product, which is usually manufactured without a licence from the innovator company and marketed after expiry of the patent or other exclusivity rights. The term should not be confused with generic names for APIs.

Microbiology

A branch of science that refers to microbes of all of types, including bacteria, viruses, rickettsia, protozoa, fungi and prions. Derived words (such as microbiological) have a similar meaning.

Multisource (generic) pharmaceutical product

Multisource pharmaceutical products are pharmaceutically equivalent products that may or may not be therapeutically equivalent.

Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.

New chemical (or biological) entities

Actives that have not previously been authorized for marketing as a drug for use in humans in the country in question.

Pharmaceutical equivalents

Products are pharmaceutical equivalents if they contain the same amount of the same actives in the same dosage form, if they meet comparable standards, and if they are intended to be administered by the same route. Pharmaceutical equivalence does not necessarily imply therapeutic equivalence, as differences in the excipients and/or manufacturing process and some other variables can lead to differences in product performance.

Pivotal clinical trials

Those clinical studies that provide the significant evidence that is the basis for the decision as to the risk–benefit assessment for a particular FDC.

Product information

The information provided by the supplier of an FPP that allows prescribers and consumers to ensure the safe and effective use of drugs. If it is written especially for prescribers, it may be termed prescribing information.

Reference product

A pharmaceutical product with which the new product is intended to be interchangeable in clinical practice. The reference product will normally be the innovator product for which efficacy, safety and quality have been established. Where the innovator product is not available, the product that is the market leader may be used as a reference product, provided that it has been authorized for marketing and its efficacy, safety and quality have been established and documented.

Summary of product characteristics (SPC)

A term used in the European Union. Product information or data sheets in the European Union should be based on the approved SPC.

Well-established drugs

Actives that:

- have been marketed for at least 5 years in countries that undertake active post marketing monitoring;

- have been widely used in a sufficiently large number of subjects to permit the assumption that safety and efficacy are well known; and
- Have the same route of administration and strength and the same or similar indications as in those countries.

4. SCENARIOS

An application to register an FDC-FPP may fall into any one of the following four scenarios. These guidelines are intended to address the different requirements for each scenario.

4.1 Scenario 1.

The new FDC-FPP contains the same actives in the same doses as an existing FDC-FPP; that is it is a "generic" of the existing FDC-FPP; they are "multisource" products. The quality, safety and efficacy of the existing product have been established.

4.2 Scenario 2.

The new FDC-FPP contains the same actives in the same doses as an established regime of single entity products, and the dosage regimen is the same. Alternatively, the established regime may involve combinations of single entities and FDCs, for example, a single entity FPP combined with an FDC-FPP that contains two actives. In all cases, the established regime has a well-characterized safety and efficacy profile, and all of the FPPs used in obtaining clinical evidence have been shown to be of good quality.

4.3 Scenario 3

1. The new FDC-FPP combines actives that are of established safety and efficacy but have not previously been used in combination for this indication.
2. The new FDC-FPP comprises a combination for which safety and efficacy have been established, but that will be used in a different dosage regimen.

4.4 Scenario 4.

The new FDC-FPP contains one or more new chemical entities.

5. Balancing the advantages and disadvantages of a new fixed-dose combination

5.1 In determining whether it is rational to combine actives into a single product, there are medical, quality and bioavailability considerations.

5.1.1 *Quality* issues may be addressed by much the same criteria that apply to single-component products and it is difficult to imagine a case in which essentially the same standards would not apply.

5.1.2 *Medical* considerations are more complex and sometimes contradictory, for example, when increased efficacy is accompanied by increased toxicity. The decision as to whether to give marketing approval for a new FDC-FPP in scenarios 3 and 4 is often based on a consideration of the balance of advantages and disadvantages from the medical perspective.

5.1.3 Interpretation of the results of *bioavailability and bioequivalence* tests involves both quality and medical considerations. For example it is not acceptable that bioavailability is reduced or variable, when compared with that of single entity products, because of poor formulation, but an interaction between two actives that leads to an increased bioavailability may be one of the advantages that is taken into account when balancing advantages and disadvantages.

Balancing the advantages and disadvantages of a new FDC-FPP should form a major component of submissions pursuant to this guideline.

5.2 Submissions for marketing approval of a new FDC in scenarios 2, 3 and 4 should include a section in which the advantages of the new combination are weighed against the disadvantages. All the possible

advantages and disadvantages of the combination should be listed and discussed. The discussion should be based on the available data and on scientific and medical principles. In less well-developed nations, and particularly where there are difficulties with transport and the logistics of distribution, other matters may need to be taken into account, such as:

5.2.1 The cost of the combination as compared with the cost of individual components.

5.2.2 Evidence as to whether the new FDC will improve the reliability of supply as a result of simplified distribution procedures. Improved patient adherence may result from more reliable (continuing) availability of the FDC-FPP than of all of the components as loose combinations of single entity products.

However, issues of cost and procurement alone are not sufficient reason to approve an FDC if it has not been justified by appropriate data and on scientific and medical principles.

5.3 From a scientific or medical perspective, FDCs are more likely to be useful when several of the following factors apply:

5.3.1 There is a medical rationale for combining the actives.

5.3.2 There is an identifiable patient group for which this combination of actives and doses is suitable therapy. The larger the patient group in question, the more significant is this factor. It is not appropriate to combine actives that separately treat conditions that do not commonly coexist.

5.3.3 The combination has a greater efficacy than any of the component actives given alone at the same dose.

5.3.4 The incidence of adverse reactions in response to treatment with the combination is lower than in that response to any of the component actives given alone, for example as a result of a lower dose of one component or a protective effect of one component, and particularly when the adverse reactions are serious.

5.3.5 For antimicrobials, the combination results in a reduced incidence of resistance.

5.3.6 One drug acts as a booster for another (for example in the case of some antiviral drugs).

5.3.7 The component actives have compatible pharmacokinetics and/or pharmacodynamics. See comments under Pharmacokinetics and pharmacodynamics below (section 6.6.2).

5.3.8 Therapy is simplified, particularly when the existing therapy is complex or onerous (e.g. because of a “high tablet load”).

5.3.9 One of the ingredients is intended to minimize abuse of the other ingredient (e.g. the combination of diphenoxylate with atropine, or buprenorphine with naloxone).

5.3.10 The active pharmaceutical ingredients are chemically and physic chemically compatible or special formulation techniques have been used that adequately address any incompatibility.

5.3.11 Other potential advantages of FDCs over single entity products given concurrently in the same dose may include:

5.3.11.1 Convenience for prescribers and patients.

5.3.11.2 Better patient adherence.

5.3.11.3 Simplified logistics of procurement and distribution.

5.3.11.4 Lower cost.

These factors are important, but there may not necessarily be evidence to support them; they may be more significant when there is specific evidence available to support a particular case.

5.4 From a scientific or medical perspective, FDCs are less likely to be useful when one or more of the following factors apply:

5.4.1 The component actives are normally separately titrated to meet the patient’s needs. Consequently:

5.4.1.1 Either the doses of the components, and/or the ratio of doses, typically differ from patient to patient, and/or

5.4.1.2 Patients are likely to be taking different doses at different stages of treatment (for example initial treatment compared with long-term treatment).

These two factors are particularly significant when one or more of the actives has a narrow therapeutic index and/or a steep dose– response curve in the therapeutic range.

5.4.2 There is a higher incidence or greater severity of adverse reactions to the combination than with any of the ingredients given alone, or there are adverse reactions not seen in response to treatment with any of the individual ingredients.

5.4.3 There are unfavourable pharmacokinetic interactions between the ingredients, for example when one drug alters the metabolism, absorption or excretion of another. However, see comments under Pharmacokinetics and pharmacodynamics below (section 6.6.2) concerning circumstances in which such interaction is intended.

5.4.4 Dose adjustment is necessary in special populations, such as in people with renal or hepatic impairment.

5.4.5 The product (tablets or capsules), is so large that patients find it difficult to swallow.

6. Data requirements for marketing authorization of fixed-dose combination finished pharmaceutical products

6.1 General

6.1.1 The framework for issuing a marketing authorization for an FDC-FPP is the same as that for single entity FPPs and is stipulated by Part I of this Compendium of guidelines.

6.1.2 Data requirements for marketing authorization of FDC-FPPs depend broadly on the scenario into which the application falls (see sections 4.1–4.4 above). Table 1 summarizes these differences.

However, each application should be considered on its own merits using scientific judgement and logical argument.

6.1.3 All applications to register an FDC-FPP should include a draft "product information" or "summary of product characteristics" for indicated diseases, and any package information leaflet or patient information. See the more detailed discussion below (section 7).

Summary of requirements for the various scenarios

This table is a list of the most likely set of requirements for marketing authorization of an FDC-FPP in each scenario. However, each application should be considered on its own merits in relation to data requirements, using scientific judgement and logical argument. Some of the data may be provided in the form of literature studies.

Table 1: Requirements for marketing authorization of an FDC-FPP in each scenario

Requirement	**Scenario 1**	**Scenario 2**	**Scenario 3**	**Scenario 4**
Rationale for the combination	Not usually	Not usually	√	√
Balancing advantages and disadvantages of the combination	Not usually	Not usually	√	√
Marketing status in other countries	√	√	√	√
Analysis of literature data in the submission	Possibly for pharmaceutical development	Possibly for pharmaceutical development	√	√
Pharmaceutical development studies	√	√	√	√
GMP certification of sites of manufacture	√	√	√	√
A full quality data set	√	√	√	√

Requirement	Scenario 1	Scenario 2	Scenario 3	Scenario 4
Bioavailability data[a]	Not usually	Not usually	Sometimes	√
Bioequivalence data	√	√	Sometimes	Sometimes
Preclinical pharmacology and safety	Not usually	Not usually	Sometimes	√
Clinical safety and efficacy	Not usually	Not usually	√	√
Product information	√	√	√	√
Plan for passive post-marketing surveillance	√	√	√	√
Plan for active post-marketing surveillance	Not usually	Not usually	√	√

6.1.4 A full quality data set is required in all scenarios (see 6.3 below).

6.1.5 In general, preclinical or clinical safety and efficacy data are not required in *scenario 1*. If the risk–benefit assessment has been found to be acceptable for an FDC, then new brands may be approved on the basis of bioequivalence with the brand(s) used in pivotal clinical trials.

The applicant may, however, be asked to establish that a risk–benefit assessment has been conducted and found acceptable if, for example the drug regulatory authority to which the application is submitted is not convinced that this is the case or does not have access to the data.

6.1.6 If the FDC directly substitutes for an established regimen of single entity products, in relation to both actives and doses and for the same indication(s), a bioequivalence study may provide adequate evidence of safety and efficacy. This is *scenario 2*. The established regimen should have well-characterized safety and efficacy.

6.2 Good manufacturing practice

Evidence of GMP compliance for all the API and FPP sites should be provided in Module 1 of the PD.

Only medicines manufactured, packed and quality controlled at sites compliant with the current principles of Good Manufacturing Practice (GMP) as prescribed by PPB will be considered for registration.

6.3 Quality

6.3.1 In relation to quality, very similar principles apply to FDC-FPPs as apply to single entity products. However, there are additional complexities arising from the need to consider two or more actives instead of one. These complexities are principally, but not exclusively, related to assay, stability, physicochemical properties (for example dissolution rate) and bioavailability/ bioequivalence. Consequently, the following considerations (and others) may be pertinent.

6.3.2 Pharmaceutical development studies are especially important for FDC-FPPs because they are technically more demanding than single-component products. Issues that are specific to the development of FDC-FPPs include:

6.3.2.1 Chemical and physicochemical compatibility of the APIs in an FDC with one another as well as with possible excipients.

6.3.2.2 The degradability of each API under stress conditions in the presence of the others.

6.3.2.3 Uniformity of content of each active prior to compression (tablets) or filling (for instance capsules, sachets and suspension dosage forms). This study determines whether mixing during manufacture is adequate.

6.3.2.4 Analytical procedures. These should be validated for each active in the presence of the others during development of analytical methods for quality control of the finished product, stability testing and dissolution testing.

Validation should be conducted for each active in the presence of the others and in the presence of related synthesis (process) impurities and potential degradation products. In the case of high-performance liquid

chromatography (HPLC) (a common analytical technique), possible interference by degradation products in the assay of the active can usually be controlled by peak purity testing.

6.3.2.5 The dissolution rate of each active in pilot formulations. Multipoint limits should normally be established for routine quality control of each active. For some FDCFPPs, different dissolution media may be acceptable for the different actives.

6.3.2.6 Different assay procedures may be necessary for the different actives in the finished product, and for different purposes (e.g. dissolution testing may be needed rather than stability testing).

6.3.3 For solid dosage forms a test and limit for content uniformity should be applied to any active that is present at a weight of ≤25 mg or when the API comprises 25% or less of a dosage unit.

Typically, when any one API is present at less than 25 mg or less than 25% of the weight of a dosage unit, all of the actives are subjected to content uniformity testing.

If a solid dosage form is not subject to content uniformity testing, for example because all of the actives are present at a weight of greater than 25 mg and greater than 25% of the weight of a dosage unit, there should be a test and limit for mass variation.

6.3.4 Acceptance criteria for impurities in FDC-FPPs should be expressed with reference to the parent API (and not with reference to the total content of APIs). If an impurity results from reaction between two APIs, its acceptance limits should be expressed in terms of the API that represents the worst case. If available, a reference standard should be used to quantify the degradation product in percentage mass/mass with respect to the parent API. Alternatively, and if justified, other quantitative techniques that are described in *Impurities in new drug products*(revised) ICH-Q3B(R) (2003), may be applied.

***Note*:** there should be an approximate mass balance. Together with the remaining active, degradants expressed with reference to the parent compound should sum to approximately 100% of initial strength.

6.3.5 The specifications and defining characteristics of the product should be based on the most vulnerable active. For example expiry dates should be based on the stability of the least stable active.

6.3.6 In setting specifications, relevant pharmacopeial monographs, WHO guidelines, ICH guidelines and PPB guidelines should be taken into account.

6.3.7 Specifications in addition to those in pharmacopoeias may be necessary for APIs in some cases, for example for particle size, residual solvents and synthesis-related impurities that are not covered by relevant monographs.

6.4 Bioavailability and bioequivalence

6.4.1 Data on bioequivalence provide a bridge between two pharmaceutical equivalents (see Glossary) when safety and efficacy data are available for one of the FPPs, but not for the other. By demonstrating that the two products lead to the same profile for plasma concentration over time, available safety and efficacy data for one of the products can be extrapolated to the other. The two products being compared may be different brands, or different batches of the same brand, for example when manufactured by different methods, at different sites or according to different formulations.

6.4.2 Data on bioequivalence may also be important when the same FPP is administered under different circumstances, for example before or after food, in different patient populations (such as children versus adults), or by different routes of administration (such as subcutaneous versus intramuscular injection).

6.4.3 In the context of these guidelines, an additional application of bioequivalence studies is in scenario 2 in which safety and efficacy data on single entity products given concurrently may be extrapolated to an FDC-FPP, provided that all of the conditions described elsewhere in these guidelines are met.

6.4.4 Evidence as to bioequivalence is required for *scenarios 1* and *2*, and sometimes for *scenarios 3* and *4*, for example when there are major differences between the formulation and/or method of manufacture of the product to be registered and that used in pivotal clinical trials.

6.4.5 If a study of bioequivalence finds that the two treatments are bioequivalent, it may be assumed that any pharmacokinetic interactions between the actives were the same, even if one treatment comprised an FDC-FPP and the other comprised separate products.

6.4.6 Data on absolute bioavailability are usually required in scenario 4, i.e. comparison of the area under the curve for plasma concentration over time after an intravenous injection with that after administration of the dosage form to be marketed, for example a tablet given orally.

6.4.7 A decision as to whether it is necessary to conduct a study of the effect of food on the bioavailability of an FDC-FPP should be based on what is known of the effect of food on the individual actives, and any relevant recommendations in the product information for the single entity products.

The effect of food should normally be studied in scenario 4.

6.4.8 Recommendations as to the conduct and analysis of bioequivalence studies are provided in the guideline on bioequivalence requirements (Part III) of Compendium of Guidelines on medicines evaluation and registration in Kenya)

6.5 Preclinical pharmacology and safety

6.5.1 Preclinical data are not normally required in scenarios 1 and 2. Data may, however, be required in some circumstances, for example if an unusual excipient is included in the formulation or if the impurity profile differs significantly from that of reference products.

6.5.2 Preclinical data will be required in scenario 4 as for any new chemical entity. The standard of evidence should be the same as for any new chemical entity.

6.5.3 In scenario 3, preclinical studies may not be required if all the actives have been extensively used in humans in the same combination for a long period and the safety of the combination has been well demonstrated. Bridging studies may be appropriate in some cases, for example for a new ratio of doses.

6.5.4 If the safety of the combination in humans has not already been demonstrated (i.e. in scenarios 3 and 4), preclinical studies should be conducted on the actives administered in combination in order to investigate possible additive or synergistic toxicological effects.

The preclinical data that are required in scenarios 3 and 4 will vary according to the data that are already available. For example, by definition in scenario 3, the safety and efficacy of each active will have already been established, but that of the combination will not. In scenario 4, the safety and efficacy of one or more of the actives may already have been established, but not those of all the actives or of the combination.

6.5.5 When preclinical data are required, the studies should aim to determine both the pharmacological and the adverse effects that may be expected from the combination of actives during clinical use.

6.5.6 As a general rule, preclinical studies on the combination should be performed with the actives in same the ratio as in the FDC-FPP in question. If this is not the case, the applicant should explain and justify the proportions used. A comparison of the systemic exposures in animals and humans will be relevant.

6.5.7 In the absence of relevant WHO guidelines, the ICH preclinical guidelines in Table 4 may be used as source of guidance.

6.5.8 Preclinical studies should comply with a suitable code of good laboratory practice (GLP); see, for example *Handbook*: *Good laboratory practice*: *Quality practices for regulated non-clinical research and development*. World Health Organization (2001)

6.6 Microbiological preclinical studies

In general, this section is applicable to scenarios 3 and 4, but not to scenarios 1 and 2. There may be some exceptions, for example microbiological data may be appropriate in scenarios 1 and 2 if a different pathogen or resistance pattern is encountered.

6.6.1 In scenarios 3 and 4, when a new combination is proposed for an antimicrobial indication, microbiological studies may be needed to determine the advantage of the FDC over the individual active moieties against relevant pathogen(s), and especially when clinical trials of monotherapy are inappropriate or unethical.

6.6.2 Data from microbiological preclinical studies of FDCs are particularly useful when clinical trials of monotherapy are inappropriate or unethical.

6.6.3 Data from the following types of study should normally be available for the combination:

6.6.3.1 Characterization of microbiological activity in vitro and in vivo against laboratory strains and clinical isolates of the targeted pathogen(s), including those strains in the relevant geographical regions.

6.6.3.2 Characterization of microbiological activity in appropriate animal models of infection with the targeted pathogen(s).

6.6.3.3 If possible, characterization of the mechanism by which the actives exhibit additive or synergistic microbiological activity against the targeted pathogen(s).

6.6.3.4 The potential for antagonistic effects between the actives.

6.6.3.5 The potential for development of resistance by target pathogens.

6.7 Clinical efficacy and safety

This section is in general applicable to *scenarios 3* and *4* but not to *scenarios 1* and *2*. Bridging studies may sometimes be appropriate in scenario 3, for example for a new ratio of doses or a longer duration of treatment.

6.7.1 **General principles**

6.7.1.1 The risk–benefit assessment for a new combination may be based on data generated using *either* the components given as single entity products concurrently *or* the FDC as a single FPP.

6.7.1.2 Any theoretical advantages of a particular combination should be confirmed by means of efficacy studies. The risk–benefit assessment should not be based on theoretical considerations only, or on extrapolation from other data.

6.7.1.3 If the actives in an FDC are intended to relieve different symptoms of a disease state, it is a prerequisite that these symptoms commonly occur simultaneously at a clinically relevant intensity and for a period of time such that simultaneous treatment is appropriate. Occurrence of the individual symptoms in isolation should not be indications for the FDC.

6.7.1.4 Clinical studies should be designed to determine whether the combination has an advantage over the component actives given alone in a substantial patient population. The data should demonstrate that each active contributes to the therapeutic effect of the combination.

It may not be essential to show that all of the components have efficacy when administered as single entities; for example clavulanic acid has little or no antimicrobial activity when given alone, but it enhances the efficacy of beta-lactam antibiotics.

6.7.1.5 In situations where comparative clinical trials are not feasible, for example when monotherapy is inappropriate or is unethical, an aggregate of clinical and preclinical data may be substituted. Such data may include:

6.7.1.5.1 Historical clinical data, preferably at an exposure comparable to that for the proposed FDC.

6.7.1.5.2 Bridging pharmacokinetic data.

6.7.1.5.3 Preclinical pharmacology and/or toxicology data.

6.7.1.5.4 In vitro data (e.g., microbiological studies).

6.7.1.6 If the FDC is available in more than one strength or ratio of doses, there should be a risk–benefit assessment for each combination.

6.7.1.7 The choice of comparators for the purposes of safety and efficacy studies should be justified. They should normally represent the recognized treatment for the indication in question. As far as possible, comparators should be licensed products with well-established safety and efficacy profiles and of established quality. Unapproved or novel combinations should be avoided as comparators as they may introduce new efficacy or toxicity characteristics and thus complicate assessment of the combination under test.

6.7.1.8 If the combination is intended for long-term use, data on safety in patients will normally be required for 6 months or longer.

6.7.1.9 If one or more of the component actives has an established use and dosage regimen in indications unrelated to the indications of the FDC, existing experience as to its safety may nevertheless be taken into account, bearing in mind the relative doses for the two sets of indications.

6.7.1.10 End-points in clinical trials should be such as to characterize the advantages and disadvantages of the combination.

For example, for a combination designed to reduce the development of drug resistance, end-points might include the frequency of new drug resistance as well as the overall clinical outcome.

6.7.1.11 Parallel group comparisons are one means of demonstrating a therapeutic effect. A parallel placebo group should be included if feasible and if consistent with the indications under treatment. Multi factorial designs are another means by which it may be possible to demonstrate that a combination is superior to the individual actives.

6.7.1.12 In some cases, studies have to be specifically designed to confirm the minimal effective dose and the usual effective dose of the combination. Multiple dose-effect studies may be necessary.

6.7.1.13 The design and analysis of studies of efficacy and safety should consider (among other things) whether the combination is indicated as first- or second-line therapy.

6.7.1.14 In general, all of the actives in a combination should have a similar duration of action. If this is not the case, the applicant should explain and justify the combination.

6.7.1.15 In general, the actives in a combination should have similar pharmacokinetics. If this is not the case, the applicant should explain and justify the combination.

6.7.1.16 If there is an increase in the number or severity of adverse reactions to the FDC as compared with those in response to the individual actives given alone, evidence and argument should be presented showing that the advantages of the combination outweigh the disadvantages. These should be included in the section of the submission entitled “Balancing the advantages and disadvantages of a new FDC”.

6.7.1.17 Data generated in clinical safety and efficacy studies should comply with the WHO *Guidelines for good clinical practice (GCP) for trials on pharmaceutical products* (1995).

6.7.2 **Pharmacokinetics and pharmacodynamics**

This section is generally applicable to scenarios 3 and 4, but not to scenarios 1 and 2. In scenarios 1 and 2, the information described below will usually already be available.

6.7.2.1 In general, it is desirable that there be no pharmacokinetic or pharmacodynamic interactions between the components of a combination. However, there are circumstances in which such an interaction is intentional and may even contribute to the therapeutic outcome.

For example:-

6.7.2.2 Ritonavir boosts the activity of protease inhibitors.

6.7.2.3 Carbidopa and benserazide both reduce decarboxylation of levodopa in the gut wall, and consequently reduce the dose of levodopa that should be administered.

6.7.2.4 Clavulanic acid reduces bacterial hydrolysis of beta lactam antibiotics and consequently both increases the concentration and prolongs the duration of effectiveness.

6.7.2.5 Tests should be conducted to elucidate any pharmacokinetic or pharmacodynamic interaction between the actives in a combination. Some interactions may be predictable from pharmacokinetic and enzyme profiles, but should be confirmed by experiment. Any interaction should be quantified so that its effect on safety and efficacy is either predictable or (preferably) has been tested in a clinical study. This includes competing metabolic effects and effects on gastrointestinal efflux mechanisms or on renal excretion or

re-absorption. Interactions may be additive, synergistic or antagonistic.

6.7.2.6 If there is an unintended pharmacokinetic interaction between the actives, it should be demonstrated that the therapeutic advantages of the combination outweigh any disadvantages resulting from the interaction. Relevant argument and cross-references to data should be included in the section that discusses the balance between the advantages and disadvantages of the combination.

6.7.3 **Additional guidelines for scenario 3**

6.7.3.1 The risk–benefit assessment for a new combination may be based (at least in part) on a demonstration of the clinical non-inferiority of the combination to another product licensed for the same indication. See Appendix 4, entitled *Superiority, equivalence and non-inferiority clinical trials*, for more information.

6.7.3.2 Pharmacodynamic studies for new combinations should normally be conducted at several dose ratios of the actives unless the applicant can provide justification for not doing so.

6.7.4 **Additional guidelines for scenario 4**

6.7.4.1 When an FDC-FPP contains an active that is a new chemical entity, data requirements are the same as for any new chemical entity. In some circumstances, some of the preclinical and clinical data on safety and/or efficacy may have been generated

from studies on the combination rather than on single entities, for example when one active confers a protective

effect in relation to adverse reactions or when the actives act synergistically.

6.7.4.2 Dose-finding monotherapy studies should normally be conducted for the new chemical entity before commencing studies of combination therapy, unless the new chemical entity is not intended to have activity when used alone (such as clavulanic acid). Alternative approaches may be acceptable if they can be justified.

6.7.4.3 The pharmacokinetics and enzyme profile of any new chemical entity should be fully characterized, including prediction of possible interactions and pharmacokinetics in children if the new chemical entity could be used in that population (see also section 7.6.6 on *Paediatric dosage forms*).

6.7.5 **Superiority, equivalence and non-inferiority trials and fixed-dose combinations**

Appendix 4 defines superiority, equivalence and non-inferiority trials and makes some general points concerning different types of study.

More information can be found in the Committee for Medicinal Products for Human Use (CHMP) guidelines in Table 3.

6.7.5.1 In the context of FDCs, equivalence trials are largely confined to bioequivalence studies.

6.7.5.2 An FDC-FPP should be shown, directly or indirectly, to be superior to the component actives given as single entity treatments.

Only a superiority trial can give the necessary statistical confidence. Submissions should discuss both the statistical significance and clinical relevance of the results. Any alternative form of evidence that purports to address the same issues, for example one that concerns a dose–response surface, must be explained and justified with appropriate statistical confidence.

6.7.5.3 In clinical trials that are intended to test for superiority and/or non-inferiority, the choice of comparator should be carefully considered and will depend in part on the medical and ethical circumstances. The comparator may be:

6.7.5.3.1 The treatment whose risk–benefit profile is best supported by evidence or is at least well established.

6.7.5.3.2 One or more of the actives in the FDC given as a single treatment.

6.7.5.3.3 A placebo.

6.7.5.3.4 Depending on the claim, superiority or non-inferiority should be demonstrated for each specified clinical outcome. For example, if the claim is less bone marrow depression, but similar efficacy, a non-inferiority outcome should be demonstrated for efficacy and a superiority outcome for safety.

6.7.6 **Paediatric dosage forms**

6.7.6.1 Different FDC-FPPs may be needed in paediatric populations from those needed in adults because of differences in pharmacokinetic and pharmacodynamic profiles of the actives, and for reasons of palatability. The doses of each active may need to be lower or higher, and the appropriate dose ratio may be different.

Scenarios 1 and 2

6.7.6.2 In scenarios 1 and 2, when the combination of actives and doses has already been shown to be safe and effective in the paediatric population, a bioequivalence study in adults may be extrapolated to the paediatric population provided that the pharmacokinetics of all actives are well-established in both populations and it is known that there are no differences that could affect the outcome of the bioequivalence study.

Extrapolation of bioequivalence data between age groups should be justified in these terms.

Scenarios 3 and 4

6.7.6.3 If the FDC is indicated in a paediatric population, but the combination of actives and doses has not been shown to be safe and effective in this population, suitable doses of the actives given in combination should be established. In some cases, it may be necessary to do this in more than one age group (see table 2 below).

Table 2: Paediatric populations

Paediatric populations	
Neonate	Birth to under 1 month
Infants	1 month to under 2 years
Children	2 years to under 12 years
Adolescents	12 years to under 16 years

From the age of 16 years, individuals are considered to be adults in the context of these guidelines.

6.7.6.4 The pharmacokinetic profile of each active should be established in the age groups for which the FDC is indicated.

6.7.6.5 If it is possible to define target plasma concentrations in both adults and the paediatric population for an FDC that has established safety and efficacy in adults, then it may be possible to define suitable doses in the paediatric population on the basis of pharmacokinetics. The task is easier for actives that have the same target concentrations in adults and the paediatric population, such as antimicrobials that have established minimum inhibitory concentrations (MICs) and established safety at these concentrations.

6.7.6.6 When defining target plasma concentrations in the paediatric population, possible differences in the concentration–effect relationship should be taken into account.

6.7.6.7 If safe and effective use of the FDC has not been established in any age group, and extrapolation between groups is not possible based on pharmacokinetic data, then new clinical, and possibly also preclinical, safety and efficacy data should be obtained.

7. Product information (or summary of product characteristics) for fixed-dose combination finished pharmaceutical products

7.1 This section of the guideline applies to all scenarios.

7.2 The product information should be an integrated evaluation of the FDC, and not a summation of the product information for each of the actives.

7.3 The rationale for use of the product should be presented in terms of the combination rather than in terms of the individual actives.

7.4 Only those indications for which each active in the FDC makes a useful contribution should be included in the product information. Each indication should be a well-recognized disease state, modification of a physiological state, dysfunctional state, syndrome or pathological entity.

7.5 For each indication there should be a statement as to whether the FDC is recommended for first- or second-line therapy.

7.6 Any pharmacokinetic and pharmacodynamic interactions between the actives should be described in qualitative and, as far as possible, in quantitative terms.

7.7 All clinically relevant interactions between the FDC and other drugs should be described, together with the resulting contraindications and precautions. Any deviations from expected interactions known for the single components should be highlighted.

7.8 When safety experience with the FDC is limited in comparison with that for the individual components, safety experience from clinical trials and

post marketing experience should be presented for both the FDC and the individual components, and should be identified as such.

7.9 If the safety profile for the combination is different to that for the individual actives, this should be highlighted. For example a combination of a fibrate and a statin might carry a risk of more frequent or more severe rhabdomyolysis than for either individual active.

8. Post marketing studies and variations

8.1 Post market monitoring of safety is an important part of the role of both drug regulatory authorities and manufacturers. It is especially important when there are unresolved concerns regarding safety, and when a new product is intended for wide community use, as for example a new antimicrobial FDC-FPP for use in the treatment of tuberculosis, malaria or HIV/AIDS. See WHO's *importance of pharmacovigilance: safety monitoring of medicinal products* (2002). Manufacturers should have (and use) written operating procedures for continuous assessment of the safety and utilization of their products following marketing authorization; SOPs can be examined during a GMP inspection.

For antimicrobials, monitoring of patterns of resistance is an important component of pharmacovigilance. Note also that pharmacovigilance outcomes can differ with diet, ethnicity, comorbidity and other factors.

8.2 For scenarios 1 and 2, passive surveillance (spontaneous reporting) would usually be acceptable. For scenarios 3 and 4, additional active (prospective) surveillance should be considered, especially when there is an outstanding safety concern. For more information, see the draft ICH guideline Pharmacovigilance planning (Table 5), or later updates thereof.

To ensure that drug regulatory authorities are aware of proposed changes to product information, it is recommended that marketing approval letters contain this statement:

"The product information may not be altered without prior approval, except for safety updates that further restrict use of the product. Any such safety-related changes should be notified to [name of regulatory authority] within five days of making the change."

8.3 Variations to pharmaceutical aspects of registered FDC-FPPs are subject to the PPB guidelines on variations to registered products.

To ensure that drug regulatory authorities are aware of proposed variations, it is recommended that marketing approval letters contain this statement:

"No changes may be made to the product without prior approval, except for changes of the type listed in [name of regulatory authority]'s policy on 'Changes to pharmaceutical aspects which may be made without prior approval'. Conditions in that policy apply."

9. Guidelines for co-packaged fixed-dose combinations

9.1 A co-packaged product consists of two or more separate pharmaceutical products in their final dosage form that are packaged together for distribution to patients in the co-packaging.

9.2 Co-packaged products may fall into any of scenarios 1 to 4. The data requirements for each scenario are the same as those listed in Table 6 of this Annex.

9.3 A full quality data set is required for all components of co-packaged pharmaceutical products, except for any component that already has marketing authorization in which case more limited requirements apply (see below).

9.4 If one or more of the pharmaceutical products already has marketing authorization, then the additional quality information to support co-packaging of those pharmaceutical products will typically be limited to data on stability of the products in the co-packaging.

However the manufacturer of each component pharmaceutical product should provide an assurance that the product as used in co-packaging

will be identical in formulation and method of manufacture to the one that already has marketing authorization. This is especially important when the manufacturer of a component is not the manufacturer of the co-packaged product.

9.5 Submissions concerning co-packaged pharmaceutical products should take into account the Guidelines on packaging for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report.* Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902), Annex 9.

PART VII:

GUIDELINES ON PROCEDURAL ASPECTS FOR APPLICATIONS FOR MARKETING AUTHORIZATION OF PHARMACEUTICAL PRODUCTS

ABBREVIATIONS AND ACRONYMS

BMR	-	Batch Manufacturing Record
PPB	-	Pharmacy and Poisons Board
EAC-MRH	-	East African Community Medicines Regulatory Harmonization
DPER	-	Product Evaluation and Registration
EMA	-	European Pharmaceutical products Agency
FEAPM	-	Federation of East African Pharmaceutical Manufacturers
GCP	-	Good Clinical Practice
GMP	-	Good Manufacturing Practice
ICH	-	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
MA	-	Marketing Authorization
MAH	-	Marketing Authorization Holder
TWG	-	Technical Working Group
WHO	-	World Health Organization

1.0 INTRODUCTION

The guideline covers the steps that are followed from the submission of a dossier to the final outcome, the timeframe and procedure, where necessary the conditions of marketing authorization of a particular product.

2.0 SCOPE

The guideline is applicable for all types of application submitted to PPB that include new application, renewal of application and application for variation of a registered pharmaceutical product.

3.0 TYPES OF APPLICATIONS

3.1 The applications are classified into new application, application for variation of a registered pharmaceutical product and renewal application/ re-registration Application.

3.2 A new application is an application for registration of a pharmaceutical product that is intended to be placed on the market for the first time. A new application may only be made by the applicant and he shall be the person who signs the application form.

3.3 A new application for registration shall include submission of relevant documentation as provided in the main guidelines for registration of pharmaceutical products in use.

4.0 GENERAL REQUIREMENTS AND APPLICATION PROCEDURES FOR PHARMACEUTICAL PRODUCT REGISTRATION

5.1 All applications and supporting documents shall be in English. All submitted documents which are in any language other than English must be accompanied by a certified or notarized English translation.

5.2 The responsibility of applying for product marketing authorization rests with the company responsible for the introduction of the product into the Kenyan market, i.e.: the Marketing Authorization Holder (MAH).

5.3 Applications must be duly completed and supported by all of the required documents i.e. Module I to Module V in accordance with the ICH Common Technical Document (CTD) for registration of pharmaceutical products. The submitted application will be screened

for completeness within 90 working days. Dossiers which are incomplete will not be accepted for evaluation.

5.4 A dossier is a file that contains detailed scientific information on the chemistry, formulation, manufacturing, quality control and non-clinical and clinical studies that demonstrates quality, safety and efficacy of active pharmaceutical ingredient(s) and the corresponding finished pharmaceutical product.

Different sections of the dossier shall be distinctly marked and page numbered in the style: page x of y and have a table of contents indicating the sections and page numbers. Where information is required in the application forms its location shall be cross referenced in dossier. Information for each section shall be printed on both sides of an A-4 paper which will be arranged sequentially on a 1.00 mm or more diameter stainless spring and clamped with a stainless-steel binder of not less than 1.0 mm thick in an A4 expandable spring file. The file shall be of cardboard or paper material of not less than 600gsm.

5.5 The covering letter shall be submitted in hard copy and the entire dossier on a CD-ROM or the entire application be electronically submitted to PPB portal.

5.6 Data shall be presented on A4 and 80g/m^2 paper with readily readable letters of at least 12 font sizes. Every page shall be numbered sequentially. Extension sheets, tables, diagrams and other supporting documents shall as far as possible be of the same size, well annotated, numbered and appropriately cross-referenced.

5.7 Application must be accompanied by two samples of the finished product as packaged for sale. PPB may request for additional samples when need arises.

5.8 The processing fees and/or charges as prescribed by PPB must be paid at the point of submission of the application.

5.0 PROCESSING OF APPLICATIONS (MANAGEMENT OF APPLICATIONS)

5.1 Upon acceptance of an application, an acknowledgement for the receipt of the application will be issued within and a reference number will be generated. The reference number shown in this acknowledgement should be used in all subsequent correspondences relating to the application.

5.2 The PER Department shall complete screening of the dossier for completeness within 30 working days from receiving such application.

5.3 In the event that the dossier is incomplete, it will be rejected. The applicant will be notified of the rejection.

5.4 In case of a positive outcome during screening, PPB shall notify the MAH in writing that the screening has been successfully completed and place the dossier in the evaluation queue.

5.5 Review of application for marketing authorization of a product will follow the appropriate evaluation queue. Priority review may be granted where the product is intended for treatment of a serious or life-threatening disease. Evaluation of priority product shall be carried out within 6 months from receiving the application.

5.6 Evaluation of the application shall be carried out within 12 months from receiving the application.

5.7 Abridged evaluation will be carried out to pharmaceutical products that are registered in any of the agreed benchmark regulatory agencies.

5.8 During product evaluation, PPB may request for further information and additional supporting documents from the applicant. This shall be considered as the first round of evaluation.

5.9 Applicant should make available such information or documentation requested after the first round of evaluation within 180 calendar days from the date of receipt of the request.

5.10 Applicant should make available any information or documentation requested after subsequent rounds of evaluation within 120 calendar days from the date of receipt of the request.

5.11 If no response is received from applicant after the timelines described in 5.9 and 5.10 above, the clock stops and the application will be cancelled if no formal request for extension of deadline has been made

to PPB. A new application will have to be submitted if the MAH wishes to pursue marketing authorization of the product.

5.12 Evaluation of the additional information shall be carried out within 3 months from receiving such information. This shall be considered as the second round of evaluation and subsequent submission of additional information shall be considered as third round of evaluation and so forth.

5.13 Evaluation of one application shall not exceed four rounds of evaluation with the exception of administrative queries.

5.14 The MAH will be informed of the decision of the board in writing as to whether the application has been approved or rejected.

5.15 A registration number will be given when a product is registered. The registration number is specific for the product registered as specified in the registration documents. A certificate of registration shall be issued for the registered product.

5.16 For a product to be issued MA, it must be manufactured in a GMP compliant facility and studies conducted following GCP.

6.0 MAINTENANCE OF MARKETING AUTHORIZATION

6.1 The conditions for marketing authorization of pharmaceutical products are as follows:

6.1.1 The product registered with the marketing authorization number as stated in the marketing authorization certificate shall have the name, composition, characteristics, specifications and origin as specified in the marketing authorization documents.

6.1.2 The holder of the marketing authorization certificate must supply such documents, items, samples, particulars or information as PPB may require in relation to the registered product.

6.1.3 Changes in name, composition, characteristics, origin, specifications, manufacturer, packing, indications, labelling, package insert, product literature or any other particulars of the

registered product shall not be made without prior approval from PPB.

6.1.4 The labels for the registered product must comply with all of the labelling requirements as specified by the guidelines for labelling.

6.1.5 The registered product must only be indicated for use as approved by PPB.

6.1.6 The holder of the marketing authorization certificate must inform PPB of any adverse reactions or complaints on quality, safety and efficacy of the registered product immediately after he/she becomes aware of such adverse reactions or complaints.

6.1.7 The holder of the registration certificate must notify in writing to PPB of any decision to withdraw the marketing authorization of the product and shall state the reasons for the decision.

6.2 MAH shall be required to pay retention fees as specified by PPB.

6.3 The registration of a product shall be valid for 5 years or such period as specified in the registration certificate (unless sooner suspended or cancelled).

6.4 The renewal of product registration should be done not later than three months prior to expiry. Applications for renewal of registration shall be made by submitting the following:

a. Duly filled in application form for registration.

b. Batch Manufacturing Record (BMR) of a real batch manufactured within at most six months before the submission of the application.

c. Details of all changes during validity of the registration.

d. Two samples of the finished product as packaged for sale.

e. A site master file that describes the manufacturing facilities.

f. Non-refundable evaluation fee for registration of pharmaceutical product and GMP and GCP inspection fees for facilities not inspected and approved by PPB within a period specified.

7.0 CANCELLATION OR SUSPENSION OF MARKETING AUTHORIZATION

7.1 PPB may cancel or suspend the marketing authorization of any product if there are deficiencies in safety, quality or efficacy of the product or failure to comply with the marketing authorization requirements or due to changes in national policies.

7.2 Such products may not be imported and marketed in the country. The holder of the registration certificate shall immediately surrender to PPB the marketing authorization certificate upon cancellation or suspension of marketing authorization of the product.

7.3 PPB may notify other regulatory authorities on the decision taken on the respective products.

8.0 APPEALS AGAINST PPB'S DECISIONS ON PHARMACEUTICAL PRODUCT MARKETING AUTHORIZATION

8.1 For products that have been suspended and cancelled marketing authorization by PPB, MAH may make a written appeal to the PPB to review its decision.

8.2 All notice of appeals must be made within thirty (30) calendar days from the date of the notification.

8.3 MAH shall make appeal by giving grounds for review for each reason given for the rejection of his product. The grounds for the request shall be based on the information that was submitted in the product dossier. Any additional or new information that was not earlier submitted will not be accepted. PPB may review or uphold its earlier decision.

9.0 VARIATIONS IN PARTICULARS OF REGISTERED PRODUCTS

All variations to a registered product shall be made according to requirements stipulated by PPB Guidelines for Variation of Registered Human medicines.

9.1 Extension Applications

9.1.1 An extension application is an application that is a modification of an already registered medicinal products. The modification shall be such that it does not fulfil criteria for minor or major variations but is similar enough to the original product in terms of quality, safety and efficacy.

9.1.2 A marketing authorization holder may apply for extension of marketing authorization of an already registered product as an extension application. Such an application should be submitted as a new application however an abridged evaluation will be carried out.

9.1.3 Extension applications shall be applicable in the following situations:

a) Changes or addition of a pharmaceutical form from multi-dose to single-dose of the finished product or vice versa.

b) Change or addition of strength of the finished product.

c) Change or addition of a route of administration of the finished product for products of the same pharmaceutical form.

d) Inclusion of medical devices that result in change of strength, pharmaceutical form or route of administration of the finished product.

9.1.4 An extension application shall be accompanied by the following:

a. A dully filled in applicant form with the extension application box clearly marked (ticked).

b. The applicable registration fees for applications for registration of new applications.

c. A full dossier submitted in accordance to the requirements stipulated in the guidelines for submission of documentation for registration of human medicinal products.

d. A cover letter declaring the following:

i. The name and registration number of the relevant product from which the extension is applied.

ii. The marketing authorization holder for both products shall remain the same.

e. An overview of the nature of the extension being made.

f. Supporting data related to the proposed extension.

9.1.5 The final decision on whether an application meets the criteria for extension applications will lie with PPB. In case of any doubt the MAH may contact the PPB before filling for an extension application.

9.2 Duplicate Licensing

9.2.1 PPB shall authorise the same applicant to submit more than one application for a finished product when there are objective verifiable reasons on public health grounds regarding the availability of finished products to health-care professionals and/or patients, or for co-marketing reasons and/or for Export purposes.

9.2.2 Additionally, the holder of a marketing authorization can grant the use of product information to another marketing authorization holder, whereby the original marketing authorization holder acts as a contract manufacturer.

9.2.3 The assessment on whether the conditions of a duplicate application are met shall be done on a case-by-case basis, having regard to the facts of each application. The overall objectives being preservation of public health.

9.2.4 To assess whether an application refers to a particular finished product that has already been granted a marketing authorization, and consequently, whose application for a marketing authorization qualifies for a duplicate license, the composition in active substance(s) and the pharmaceutical form shall be considered. Thus, any finished product with the same qualitative and quantitative composition in active pharmaceutical ingredient (i.e. the same strength) and the same pharmaceutical form are to be considered as the same relevant product.

9.2.5 A duplicate product shall be identical in all marketing authorization requirements with the exception of brand name and any other specific

requirements on labelling. Additionally, any variation made to the original marketing authorization should be applied for the duplicate license.

9.2.6 Conditions for a Duplicate Marketing Authorization are outlined hereafter:

a. That the duplicate application shall be submitted by the same applicant that submitted and/or holds the marketing authorization/application that is being duplicated (hereafter "original marketing authorization/application").

b. That the original marketing authorization is valid. This step does not apply in case of duplicate applications that are submitted in parallel with the original marketing authorization application (i.e. in cases where the application for the original marketing authorization is still pending).

c. In cases where the duplicate marketing authorization is submitted on the basis of an informed consent application, there should be a letter of consent from the marketing authorization holder that owns the dossier that is referred to.

d. The original marketing authorizations to which the duplicate application relates has to be valid at the time of the submission of the duplicate application.

9.2.7 The applicant for a duplicate licence may fall under the following categories:

a. Applicant is the same entity that applied for the original marketing authorization.

b. Applicant belongs to the same group of companies as the applicant of the original marketing authorization.

c. Applicant is an independent entity that has agreed to placing on the market the product with the applicant of the original marketing authorization (evidence of license agreement or other agreement that can be identified are required).

d. Applicant is an independent entity whereby there are license agreements with the marketing authorization holder of the product in respect of which the duplicate is asked but not for the placing on the market of that product.

e. Applicant is an independent entity that has got an agreement to purchase and/or use data from the company that has applied for a marketing authorization for the product for the first time but there is not an agreement regarding the placing on the market of the product.

9.2.8 All documents in accordance to the guidelines on submission of documentation for new applications should be submitted however an abridged evaluation shall be applied. In addition, the following shall be submitted when making a duplicate licence application: -

a. A dully filled in application form (Annex II) with the duplicate licence box clearly marked (ticked).
b. A cover letter detailing the following: -
    i. The name of the marketing authorization holder relevant for the duplicate application.
    ii. The name of the product relevant for the duplicate application.
    iii. The proposed brand name for the duplicate license.
    iv. The proposed marketing authorization holder for the duplicate license.
c. The applicable registration fees for applications for registration of new applications.
d. For co-marketing reasons, the evidence co-marketing (contract or letter of agreement between the companies).
e. For duplicates asked on grounds of the existence of patents protecting certain therapeutic indications or pharmaceutical forms, the applicant shall provide a commitment undertaking to extend the therapeutic indication(s)/ pharmaceutical form(s) of the duplicate marketing authorization as soon as the patent restrictions no longer exist.

Alternatively, the applicant may also commit to withdraw the marketing authorization with restricted indications/pharmaceutical forms after the relevant patents are no longer in force. The SmPC shall be harmonized. The commitment letter shall be submitted alongside the Marketing authorization Application Dossier.

f. Letter of consent in the case of an "informed consent application".

PART VIII:

GUIDELINES ON NAMING OF MEDICINAL PRODUCTS

1.0 INTRODUCTION

Prescriptions and medications errors may occur partly due to medicinal products having sound-alike or look-alike brand names, unclear labeling, or poorly designed label artwork. Hence this guideline was developed in order to provide Market Authorization Holders (MAH)/applicants with clear guidance on how to choose brand names for their medicinal products.

The Pharmacy and Poisons Board (PPB) may request changes to a brand name if based on evaluation, it is deemed potential to:

a) cause confusion with the name of an existing medicine;

b) mislead as to the composition of the product or the use;

c) contravene any law locally or internationally;

d) or otherwise, unsafe.

Approval of the name does not imply that the marketing authorization holder is absolved of any responsibility in the incidence that actual or potential adverse reactions occur due to the brand name.

1.1 The Legal Framework

The Kenyan legislation in particular trade laws, patent laws or international agreements including resolution WHA31.32 on Nonproprietary Names for Pharmaceutical Substances should be taken into consideration while proposing a specific brand name.in support of this initiative, the Kenya has several legislative instruments on IPR which include: Anticounterfeit Act (2008); Copyright Act No. 12 of 2001; Industrial Property Act (IPA) No. 3 of 2001; Trade Marks Act Cap 506 (as last amended by the Trade Marks Act, 2002) and the Seed and Plant Varieties Act, Cap 326.

1.2 Intellectual Property Rights and patents

Intellectual Property (IP) is intangible property arising from human intellect that can only be protected upon expression. Like tangible property, it can be owned, administered by states, sold (assigned), leased (licensed), developed (exploited) and is usually enforceable by the law (Misati, 2009). Intellectual Property Rights (IPR) is defined as exclusive rights granted by the state giving the owner of IP the right to exclude all others from the commercial exploitation of a given invention, innovation, design or mark (Idris, 2002).

Innovation is a key driving force for economic development and competitiveness in the 21st century. Patents provide incentives for innovation, knowledge creation and transfer.

1.3 Scope

This guideline is applicable to naming of all prescription and non-prescription medicinal products as well as medicinal products of biological origin either as new applications or products already issued with marketing authorization.

The principles outlined in this guideline are also applicable to applications for variation of names of registered medicinal products.

1.4 Acknowledgments

This guideline was developed based on the European Medicines Agency's Guideline on the acceptability of names for human medicinal products processed through the centralized procedure and the Forty-Sixth World Health Assembly resolution WHA31.32 on the importance of using nonproprietary names in establishing national drug formularies.

2 CRITERIA TO BE CONSIDERED WHEN REVIEWING PROPOSED BRAND NAMES

The criteria listed below should be seen as general principles. The Board may develop additional guidance on specific topics based on experience and may apply additional requirements not listed in this document during the review of proposed brand names.

The criteria for acceptability of proposed brand names shall be based on public health concerns and in particular with regard to safety.

Applicants should ensure that the proposed name complies with the criteria outlined in this guideline before submitting an application for marketing authorization. Requirements and considerations taken during the review are outlined hereafter: -

2.1 Safety concerns and other public health concerns in brand names

The brand name of a medicinal product should not be liable to cause confusion in print, handwriting, or speech with the brand name of another medicinal product.

When assessing the potential for such confusion, the following aspects are considered:

a. The indication(s);

b. The patient population(s);

c. The pharmaceutical form(s);

d. The route(s) of administration;

e. The strength(s);

f. The setting for prescription, dispensing, and use;

g. The legal status/classification for supply:

i. Medicinal product subject to medical prescription;

ii. Medicinal products not subject to medical prescription;

iii. Medicinal products that are subject to special medical prescription;

iv. Medicinal products subject to restricted medical prescription;

v. Medicinal products that are subject to special and restricted medical prescription;

h. Orphan (designation) status;

i. New pharmaceutical forms, routes of administration, and/or strengths for the medicinal product concerned, as appropriate.

j. The degree of similarity *versus* the potential for harm to the patient in case of mix-up.

It should be noted that PPB may consider the potential for confusion of proposed brand names with the brand names of authorized, suspended, and revoked/withdrawn medicinal products in Kenya.

Additionally, PPB will consider brand names that have already been accepted by other National Regulatory Authorities.

When considering the potential for confusion with the name of a withdrawn/revoked marketing authorization, in principle, a period of 5 years should have elapsed after the official invalidity of the marketing authorization (e.g., publication in the national gazette notice, etc.). This period could be reduced (e.g., the product was not marketed in Kenya for a period preceding this 5-year period) if it can reasonably be justified by the applicant.

The period may be extended (e.g., if the withdrawal of the marketing authorization was linked to serious safety concerns and this has an impact on the potential risk to public health associated with the name) at the discretion of the board .PPB may also consider potential safety concerns and other public health concerns associated with the re-use of identical brand names.

The brand name of a medicinal product should not convey misleading therapeutic and/or pharmaceutical connotations. This also includes brand names that are similar or allude to the name of pharmaceutical companies if they are thought to be misleading and cause confusion at the level of product information.

The brand name of a medicinal product should not be misleading with respect to the composition of the product.

Consideration should be given to phonetics and the potential difficulties a proposed brand name may create in terms of pronunciation in the official languages of Kenya.

Consideration should also be given to the fact that very short brand names composed of, for instance, a string of letters, may be inappropriate to identify medicinal products in certain settings.

The use of qualifiers/abbreviations by letters as part of the brand name should in principle be acceptable on conditions.

Qualifiers consisting of a single letter or number(s) (Arabic and Roman) are discouraged, because they may be confused with the strength and/or posology of the medicinal product. However, the use of numbers may in certain cases be acceptable, e.g., vaccines. The applicant may provide a justification for their inclusion.

The potential added benefit versus its potential risk to public health in case of medication error shall be taken into consideration when considering the acceptability of a qualifier/abbreviation. The following shall be considered:

a. Whether the qualifier/abbreviation provides further information on characteristics of the medicinal product (e.g., duration of action, devices, route of administration, composition, patient population) without being misleading or provides for a differentiation, which may help healthcare professionals and/or patients to prescribe/select the appropriate medicinal product.

b. The applicability and use of the qualifier across the official languages in Kenya. Qualifiers or abbreviations should not require translation to provide further information.

c. The potential risk resulting from more complex names, adversely affecting memorability, pronunciation, and/or prescription of the medicinal product.

The brand name should not convey a promotional message with respect to the therapeutic and/or pharmaceutical characteristics and/or the composition of the medicinal product.

The brand name should not be offensive or have an inappropriate connotation in any of the official languages in Kenya.

For a medicinal product containing a prodrug, a different brand name from the brand name of the medicinal product containing the related active substance is required.

The brand name should not comprise wholly of initial letters (acronyms) or code numbers nor include punctuation marks.

The importance of other elements such as labelling and pack design should be taken into consideration as contributing factors for the safe use of a medicinal product. These aspects should be discussed at the time of the review of mock-ups.

The following are examples where labeling and pack design may play a role in the final decision on the acceptability of brand names:

a. The actual display of a brand name in the printed material may increase the level of similarity between two brand names or may convey a misleading connotation.

b. The labeling and pack design may support the meaning of a qualifier that otherwise would have been rejected.

2.2 Use of international non-proprietary names (INNs) in proposed brand names

The need for the protection of INNs is a matter that has found expression in both WHO Expert Committee reports and also in WHO's. Revised Drug Strategy as approved by the 39th World Health Assembly. It has. Been further emphasized in the resolution WHA46.19, adopted by the World Health Assembly in May 1993.

When proposing a brand name, Applicants are advised to take into consideration WHO resolution (WHA46.19), where appropriate, i.e. *"It would therefore be appreciated if brand names were not derived from international non-proprietary names (INNs) and if INN stems were not used in brand names".*

Two types of INN concerns could be considered i.e. a potential similarity with its own or different INN or the inclusion of an INN stem into the proposed brand name(s).

The Applicants are strongly advised to review INN similarity and/or INN stem inclusion before requesting that the proposed brand name(s) be considered for a medicinal product.

PPB will review the above cases on the basis of the WHO World Health Assembly resolution (WHA46.19) on the protection of INNs/INN stems to prevent any potential risk of confusion between brand names and common names.

2.3 Product-specific concerns in proposed brand names

For vaccines composed of several serotypes, when adding a new serotype, the original brand name may be kept, it is recommended that the name is then followed by the number of serotypes present. The description of serotypes present is then listed in the qualitative and quantitative composition. An example of the format of the proposed brand name follows:

Brand name + X [number of serotypes]

The same applies when different types of antigens are added. This is of particular importance in situations where both vaccines are simultaneously available on the market in order to allow differentiation of the products.

For radiopharmaceutical medicinal products, the inclusion of target organs in the brand name should be avoided in order to prevent misleading connotations should an extension of the indication include new target organs.

In principle, numbers should not be used in the name to avoid confusion with the strength. In cases where the numbers appear in the radionuclide, these should be displayed in superscript,

i.e. $^{\text{mass number}}$Element + [brand name]

Numbers included as part of commonly known abbreviations will be assessed on a case-by-case basis.

When reviewing the acceptability of brand names for orphan medicinal products, the same approach as for non-orphan medicinal products shall be applied. It is of particular importance in these cases to provide detailed information on the specific setting in which the product is dispensed and used as well as on the target population.

For non-prescription medicinal products, the use of qualifiers/abbreviations within the brand name should aid the selection/identification/differentiation of the product by the patient and should minimize the risk of inappropriate use.

In order to help self-selection and compliance by patients/consumers, it is acceptable that brand names have a positive connotation and/or be informative; labelling and pack design could be considered as contributing factors to this end. Carton and container labels are particularly critical for non-prescription medicinal products (general sale and OTC).

In case of a switch from "prescription" to "non-prescription" status of an already authorized medicinal product, it is up to the Applicant to choose whether to vary/extend the existing marketing authorization and consequently retain the same brand name or to submit a separate marketing-authorization application under a different brand name (see section 5). In exceptional cases, depending on the therapeutic context, the acceptability of the maintenance of the existing brand name may be further considered by PPB during the evaluation process.

For generic/hybrid/similar biological medicinal products, the same criteria apply as for any other medicinal products in respect to the brand name.

Special consideration should be given to the proposed brand name of a hybrid medicinal product to allow for differentiation when the latter differs in pharmaceutical form, strength, expression of active substance and/or indication from the reference medicinal product or other generics in the market.

Where the Applicant intends to use the common name or scientific name, instead of brand name, together with a trademark or the name of the marketing-authorization holder/applicant, they should take into account the following rules:

a. If an INN recommended by the World Health Organization exists for the active moiety it should be used within the name of the medicinal product exactly as published without omissions or abbreviations. All the linguistic versions of the INN, including translations officially recognized at the national level, shall be considered to be the same name. If one does not exist, the usual common name should be used.

b. If a Modified INN (INNM) recommended by the World Health Organization exists for the active moiety, it should be used within the name of the medicinal product exactly as published without omissions or abbreviations.

c. Where the active moiety is an unpublished INNM the name of the medicinal product should be that as agreed by users of INNs (pharmacopeia, regulatory bodies, stakeholders), in accordance with the WHO INNM working document 05.167/3.

d. The 'name of the MAH' within the name of the medicinal product should correspond to all or part of the official name of the MAH as presented in the proof of establishment of the applicant/MAH.

e. When the Name of the MAH and the INN name are used together, the INN name should be more prominent.

f. For consistency reasons, ease in prescription by healthcare professionals and database entries, punctuation marks between the INN and the name of the Company/trademark are not acceptable (with the exception of fixed combinations, where multiple INNs should be clearly separated by slash '/').

g. The proposed name should either be a brand name or the common name accompanied by a trademark or the name of the MAH.

h. The registration of trademarks similar to INNs, or including well-established stems, is not allowed to be used in or as trademarks.

The brand name of a fixed combination medicinal product should be sufficiently different from those of the individual active substances and/or those of other fixed combinations containing the same active substance(s).

The whole brand name of the individual active substance(s) should not be inserted into the proposed brand name for the fixed-dose combination.

As multiple applications can have an independent life (e.g. may develop a different indication at a later stage), the proposed brand names of such applications should not lead to confusion.

3 REGULATORY ASPECTS RELATED TO THE ACCEPTABILITY OF PROPOSED BRAND NAMES

Brand names for variation/extension/duplicate applications should be the same as those of the existing medicinal product. The addition of a qualifier to an already approved brand name constitutes a different brand name, which would require submission as a new marketing authorization application.

In case the applicant wants to submit a separate marketing-authorization application for, e.g., a new indication, a different brand name shall be used.

The PPB may request the MAH to change the brand name of an already approved medicinal product if the approved brand name is deemed inappropriate.

3.1 Change of the brand name

The brand name can also be changed post-authorization stage through an application for variation.

Post-authorization procedural requirements are outlined in the *Guidelines on Variations on Registered Medicinal Products*.

3.2 Report of prescription errors/medication errors due to the brand names of medicinal products:

The marketing authorization holder is responsible for reporting any adverse drug reactions resulting from:

i. Prescription errors/medication errors due to the brand name of the medicinal product (example mix up with another medicinal product resulting in an ADR).

ii. Misuse and/or abuse of a medicinal product caused by misleading therapeutic connotations of the brand name.

The ADRs should be reported in accordance with the procedures and guidance stipulated by *PPB Harmonized Compendium on Safety and Vigilance of Medical Products and Health technologies*.

Patent administration and sanctions

The Pharmacy and Poisons Board in collaboration with the Kenya Industrial Property Institute will administer this guidelines on naming of Health Products and Technologies. The Kenya Industrial Property Institute (KIPI) was established in 1989 to deal with issues of administration of IPA and Trademarks Act. The institute is responsible for the promotion of inventive and innovative activities in Kenya as well as facilitating the acquisition of technology. It grants and regulates patents for inventions. KIPI deals with both local and international patents under the relevant national and international instruments. The institute has established Patent Information and Documentation Centre (PIDOC).

Efficient enforcement of IPR has become central in the global economy, especially with the advent of Trade Related Aspects of IPR (TRIPS). The Agreement makes it mandatory for member states to provide for the minimum standards of protection (Ouma, 2009). Patents enforcement entails prevention of infringement of the rights, use of sanctions and obtaining remedies for infringement of conferred rights (Ouma, 2009). Infringement occurs when a third party reproduces, imports, sells or offers for sale a patented product without the authority of the rights holder and in the case of a process, exploits it without the authority of the rights owner (Industrial Property Act, 2001).

4 REFERENCES

1. *Guideline on the Acceptability of Names for Human Medicinal Products processed through Centralized procedure*

2. Mary Kiveu (2012) Patenting in Kenya: Status and Challenges, KIPPRA Discussion Paper No. 141 2012
3. *Ouma, M. (2009), Improving the Existing Legal Framework to Enhance Enforcement of Intellectual Property, Paper 45 References Presented at the Intellectual Property and Anti-Counterfeiting Forum, Nairobi.*

4. *Ouma, M. (2006), Public and Private Institutions in the Administration of Intellectual Property Rights in Kenya.*

5. *WHO website: http://www.who.int/en/Information on INNs: http://apps.who.int/medicinedocs/en/d/Jh1806e/5.html*

PART IX:

PROCEDURE FOR QUALIFICATION OF ACTIVE PHARMACEUTICAL INGREDIENTS MANUFACTURING FACILITIES (APIMF)

1. INTRODUCTION

Evaluation of Active Pharmaceutical Ingredients (API) is an obligatory part of the overall assessment of quality, safety and efficacy of a medicinal product. Alternate procedures for submission of API information are described in the *Guideline for Submission of Documentation for Registration of Medicinal Products* including:

a. Submission of the reference number and details of the WHO-prequalified API, together with additional supporting information.
b. Submitting a copy of the relevant Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP) issued by the European Directorate for the Quality of Medicines and HealthCare, together with additional supporting information
c. Submitting a complete ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) module 3.2.S for the API, as part of the FPP dossier submitted for evaluation.

As a means of increasing efficiency and to avoid duplication of work, PPB has decided to initiate an API certification procedure. This will enable manufacturers to procure certified APIs and thus reduce the burden of compilation of dossiers for applications for registration of new medicinal products.

This document has been prepared in order to provide guidance on supportive documents that are to be submitted in order for an API manufacturer to apply for certification of their respective APIs.

API certification should not be confused with the API master file procedure (APIMF) where by an API manufacturer is invited to provide its APIMF in support of an application for registration of FPP or a stand – alone submission.

2. ACTIVE PHARMACEUTICAL INGREDIENTS CERTIFICATION

2.1 Certification of active pharmaceutical ingredients (APIs) will be an independent procedure that identifies APIs that are of good quality and manufactured in compliance with WHO Good Manufacturing Practices (GMP). If a certified API is used in the manufacture of a finished pharmaceutical product (FPP) for which PPB registration is sought, evaluation of that FPP will be greatly facilitated by abbreviation of evaluation of the API information.

2.2 In order to become certified an API must be of good quality and manufactured in accordance with WHO Good Manufacturing Practices (GMP).

2.3 Evaluation of an API for registration has two components: assessment of the API master file (APIMF) to verify compliance with WHO norms and standards, and verification that the site(s) of API manufacture comply with WHO GMP requirements.

2.4 Registration of an API is made with specific reference to the manufacturing details and quality controls.

2.5 A certified API is therefore clearly identifiable with a specific APIMF version. An APIMF version may be altered during registration assessment, or as a result of post-registration changes. Therefore, the version number of the current APIMF will be included on the PPB List of registered Active Pharmaceutical Ingredients, to serve as a reference for the production and quality control of that API.

2.6 In addition to the registered API(s) being included in the PPB List of certified Active Pharmaceutical Ingredients, successful applicants will receive PPB Confirmation of Active Pharmaceutical Ingredient Certification for each API for which they attain certification. The confirmation will contain information on the accepted active ingredient specifications as well as the assay and related substances test methods. It may be provided by the applicant to interested parties.

2.7 There are three possible routes to API certification;

a. Full assessment of an APIMF not previously assessed by WHO.

b. Abridged assessment of a WHO prequalified API.

c. Abridged assessment of APIs that have CEPs.

3. EVALUATION OF API INFORMATION

1.1 Under the following conditions, the assessment of the API shall be limited to verification of the identity, source of API and parameters relevant to the specific dosage form:

a) In case the assessment report from the accepted APIMF is available; or
b) In case the APIMF is not (yet) accepted but API has been fully evaluated in a product approved by PPB not more than 3 years ago.

1.2 For products that have been recently submitted for registration, for which APIMF evaluation is also under way the outstanding concerns from the APIMF evaluation report shall be taken into consideration during evaluation of the FPP.

1.3 For the rest of products, i.e. for which APIMF is not submitted, the FPP evaluation shall include full evaluation of the related API(s) according to the CTD format.

1.4 APIs cannot be classified into two categories – high and low risk APIs by any single criteria, but the extent of effort and detail required for their assessment depends mainly on the track record of this API source.

1.5 In case pharmacopoeial monograph is available, the evaluation should include, whether the monograph used is actually suitable to control the quality of the substance in the context of the related medicinal product and the API manufacturing process specific to each source

1.6 Evaluation of submitted APIMFs shall be done based on the principle of First In First Out, however priority may be given to an APIMF that is used in support for multiple products submitted for registration.

4. API MASTER FILE (APIMF) PROCEDURE

Information on the preparation, control and stability of an active pharmaceutical ingredient (API) intended for use in a finished pharmaceutical product (FPP) can be provided by the API master file (APIMF) procedure. This

procedure has advantage over other options of submitting the API information in that it preserves the confidentiality of the API information.

4.1 How the APIMF procedure works

4.1.1 The FPP applicant submits the open part (non-confidential information) (OP) of the APIMF as part of the application for registration of the FPP. In so doing the applicant demonstrates that it has at least basic knowledge about the API used in the manufacture of its product.

4.1.2 The FPP applicant requests the API manufacturer to provide a Letter of Access granting the PPB permission to review the restricted part (RP) (i.e. containing confidential information) of the APIMF when evaluating the relevant FPP applied for registration.

4.1.3 In the Letter of Access, the API manufacturer should commit to informing PPB of any changes it has made to the details of either the OP or restricted part (RP) of the APIMF, and to inform the FPP applicant of any changes made or likely to be made to the preparation, control and/or stability of the API.

4.1.4 Thereafter the API manufacturer provides PPB with both the OP and the RP of the APIMF for review.

4.1.5 It is the responsibility of the FPP applicant to ensure that the API manufacturer provides PPB with the complete APIMF (i.e. both the OP and the RP).

4.1.6 PPB shall contact the APIMF holder directly if it has any questions arising from its assessment of the RP, or requires any further information about the APIMF. Once assessment has been completed (i.e. the APIMF is considered to be acceptable), the APIMF details are considered to form part of the FPP dossier.

4.1.7 Reassessment of the APIMF shall not be required when other applications for registration of FPPs using the same API are submitted provided that the API manufacturer consents and provides a Letter of Access allowing their APIMF to be used in support of a specified FPP application.

4.2 General considerations

4.2.1 Both the APIMF procedure and the API certification procedure may be used in support of an FPP application, and both procedures make extensive use of APIMFs.

4.2.2 API certification is a stand-alone procedure for API manufacturers and does not need to be applied when an application for FPP registration is made.

4.2.3 Acceptance of an APIMF within the APIMF procedure does not mean that the API is certified. However, APIMF holders who have had their APIMF accepted within the APIMF procedure may wish to build upon this acceptance and apply for API certification.

4.2.4 The same APIMF can be used as part of a submission for API certification and as part of a submission of an application for FPP registration.

5. INSPECTION OF API MANUFACTURERS

All manufacturers of APIs used in approved medicinal products should comply with GMP. API Manufacturing site requirements are as follows:

5.1. All applicants must submit a site master file (SMF) for each manufacturing site of each API and intermediate involved in the preparation of the API for which registration is sought. An SMF is a document prepared by the manufacturer containing information with respect to the production and/or control of pharmaceutical manufacturing operations carried out at a named site, and to any closely integrated operations at adjacent and/or nearby buildings. If only part of the API production is carried out at a site — such as analysis or packaging — the SMF need describe only that operation.

5.2. Each API or intermediate manufacturing site must comply with PPB GMP guidelines. Manufacturers who submit an application for registration should therefore request inspection by PPB of the relevant

manufacturing site(s) so that compliance with PPB GMP can be assessed. However, applicants whose manufacturing site(s) have already undergone a WHO Prequalification GMP inspection, or inspection within the past three years by a member of the Pharmaceutical Inspection Co-operation Scheme (PICs), evidence of this can be submitted inspection as part of their application for API prequalification, in lieu of a request for inspection by PPB.

5.3. By definition, if an API manufacturer is rated unacceptable with regard to GMP compliance, there is a risk to public health and safety. The degree of risk will depend on the nature of the GMP deficiencies and the type of API and medicinal product.

5.4. New medicinal products should not be approved by PPB unless all API manufacturers have been determined to comply with PPB GMP guidelines with respect to the manufacture of the specific API(s). An exception to this may be considered when the health benefits from a product being available are greater than the risk to public health and safety resulting from GMP non-compliance. A risk-based decision will be made on a case-by-case basis and documented.

5.5. PPB approval of existing medicinal products should be suspended if an API manufacturer is found to have an unacceptable level of GMP compliance. An exception to this may be considered when the health risk due to product unavailability is greater than the risk to public health and safety resulting from GMP non-compliance. A risk-based decision will be made on a case-by-case basis and documented.

5.6. As a default, all manufacturers of APIs used in PPB approved medicinal products should be inspected by PPB. An inspection by the PPB may be omitted when other acceptable evidence of GMP compliance is provided by the API manufacturer.

5.7. An inspection by another acceptable organisation, such as the EDQM, a PIC/S member country, the US FDA, WHO or an other PPB acceptable organization, may be considered in lieu of a PPB inspection when:

a) The inspection was conducted within the last 3 years, and

b) The scope of the inspection covered the specific API in question, and

c) The API manufacturer submits a copy of the last inspection report for review by PPB. The review must determine that the inspection was comprehensive and that the inspection report supports the final outcome.

d) Irrespective of the above, PPB reserves the right to inspect any API manufacturer if considered necessary on a risk basis.

5.8. Whether inspected by PPB or GMP compliance is based on an inspection by another acceptable organisation, on-going GMP compliance must be confirmed at least every 3 years.

5.9. API inspection conducted by PPB should be prioritised on a risk basis. The following order is provided for guidance in determining priorities:

a) Sterile APIs
b) The API is used in a number of products
c) The API is produced by fermentation
d) The sole supplier of an API
e) A new API manufacturer when the product approval process may be held up by lack of GMP evidence for the API manufacturer
f) Re-inspection when it is more than 12 months past the re-inspection due date

REVISION HISTORY

Revision No	Date	Author	Section(s) Revised	Description of the Change
1.	11.01.2022	QAO	PART III: of the guideline (GUIDELINES ON FORMAT AND CONTENT OF SUMMARY OF PRODUCT CHARACTERISTICS FOR PHARMACEUTICAL PRODUCTS)	Removal of SMPC Guideline to be placed as stand lane guideline
2.	11.01.2022	QAO	Document Number	Changed to HPT/PER/GUD/016 from PPB/HPT/PER/ /GUD/016
			Document title	Change from Guidelines on Medicines Evaluation and Registration to Compendium of Guidelines on Medicines Evaluation and Registration
			Authorization section	Changed from Registrar to CEO

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