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THE REVOLUTIONARY GOVERNMENT OF ZANZIBAR

MINISTRY OF HEALTH ZANZIBAR FOOD AND DRUG AGENCY

COMPENDIUM OF MEDICINES EVALUATION AND REGISTRATION

(Made under section 53 (1) of Zanzibar Food, Drugs and Cosmetics Act, 2006)

Second Edition

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Various stakeholders were consulted during the development and adaptation of these guidelines. The Agency would like to extend its sincere gratitude to all our esteemed stakeholders who provided us with constructive comments and inputs.

Last but not the least special thanks are extended to the ZFDA staff whose contribution on adoption of this compendium greatly appreciated, this includes:

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FORWARD

This Compendium has been adopted from East African Community (EAC) Harmonized Medicines Evaluation and Registration guideline aimed of giving guidance to Partner States – National Medicines Regulatory Authorities (NMRAs) in managing application for assessment and registration of Human Medicinal Products.

This is the second edition of the compendium was developed and formatted based on the common technical document (CTD) requirements. First Edition, was adopted '2015' from EAC which sets out procedures and requirements for the implementation of Pharmaceutical Products Registration through established CTD within the EAC NMRAs. This Compendium contains Five Modules:

Module 1: the East African Community Medicinal Products Registration administrative Requirements;
Module 2: the Quality Overall Summaries (QOS);
Module 3: the Quality Requirements for the Active Pharmaceutical Ingredients (API) and Finished Pharmaceutical Products (FPP);
Module 4: Pre-Clinical data Requirements,
Module 5: Clinical data Requirements.

The development of these guidelines were based on the focusing of existing best practice and experience within the EAC Partner States National Medicines Regulatory Authorities, technical support from World Health Organization (WHO), and on the International Conference on Harmonization of Technical Requirements for Assessment and Registration of Medicines for human use (ICH).

All pharmaceutical stakeholders are encouraged to familiarize with these guidelines and follow them strictly when preparing and submitting applications to Zanzibar Food and Drugs Agency (ZFDA) for requesting of marketing authorization of medicinal products.

Compliance to these guidelines by stakeholders will ensure that all relevant information is provided in registration dossiers submitted for marketing authorization, addition to that will facilitate efficient and effective evaluation as well as smoothening and shortening period of assessment approval and registration and it will help to avoid unnecessary queries which will result in delaying in issuance of marketing approvals

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PART I:

ZFDA 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
EAC-MRH	East Africa Medicines Registration Harmonization
EAC-NMRA	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 of Pharmaceuticals for Human Use)
PD	Product Dossier
PHIS	Pharmaceutical Health Information System
PI	Product Information
SDRA	Stringent Drug Regulatory Authority
SmPC	Summary of Product Characteristics
ZFDA	Zanzibar Food and Drug Agency

Glossary

The definitions provided below apply to the words and phrases used in these guidelines. The following definitions are provided to facilitate interpretation of the guidelines.

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*).

Local Responsible Person" means a person residing in Zanzibar or cooperate body registered in Zanzibar who has received a mandate from Market Authorization Holder to act on his behalf with regard to matters pertaining to registration of medicinal product.

Market Authorization Holder (MAH)

Is a person who holds authorization to place a medicinal product in Zanzibar and is responsible for that product.

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.

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)

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*).

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*).

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 relabeling of pharmaceuticals.

(PHIS Glossary 2009, can be found on line at:
http://phis.goeg.at/index.aspx?alias=phisglossary)

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 pharmacopoeia (or compendium)

The official recognized pharmacopoeias in the EAC-MRH project are British Pharmacopoeia (BP), European Pharmacopoeia (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.

Stringent Drug Regulatory Authority (SDRA)

A National Medicines Regulatory Authority which is strict, precise, exact with effective and well-functioning systems.

Among others, it includes regulatory authorities which are:-

- Members or observers or associates of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

  MEMBERS:

  - European Union member States (Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, The Netherlands, and United Kingdom
  - Japan
  - United States

  OBSERVERS:
  - European Free Trade Association (EFTA) represented by Swiss Medic of Switzerland, and Health Canada (as may be updated from time to time).

ASSOCIATES through mutual recognition agreements: Australia, Norway, Iceland and Liechtenstein (as may be updated from time to time).

- For medicines used exclusively outside the ICH region, positive opinions or tentative approval under any of the following three special regulatory schemes are recognized as stringent approval:-
  - Article 58 of European Union Regulation (EC) No. 726/2004
  - Canada S.C. 2004, c. 23 (Bill C-9) procedure
  - United States FDA tentative approval (for antiretrovirals under the PEPFAR programme)

- A regulatory Authority that has been agreed by the ZFDA to have an effective and well-functioning medicines regulation systems.

1. INTRODUCTION

1.1 Background

This guideline provides guidance for applicants preparing a Common Technical Document for the Registration of Medicines for Human Use (CTD) for submission to ZFDA. The document describes how to organize applications based on the International Council on Harmonization of 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. The Summaries, Quality, Non-clinical, and Clinical modules have been described in Modules 2 to 5 respectively. Applicants should not modify the overall organization of the CTD.

If not contained in the bulk of the documentation, any additional data should be included as Annex 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 ZFDA Guidelines on Procedural Aspects for Application for Market Authorization for Human Medicinal Products (Part X) **Guideline number: ZFDA……**

1.2 Scope

These guidelines will assist applicants to prepare applications to register medicinal products for human use in Zanzibar. 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.

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.

An application may be fast tracked and be evaluated within three (3) months of its submission if the product is indicated for diseases which at the time of application have no registered alternative medicine or evidence has been submitted in a motivation letter accompanying the application to show that the product has significant advantages in terms of safety and efficacy over existing products indicated for treatment or prevention of life threatening diseases.

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 ZFDA, a draft document may be included. The approved SmPC from SDRA should then be supplied to the ZFDA as they become available.

1.4.1 Prescribing information (Summary of Product Characteristics)

All prescription medicines should be accompanied by SmPC. *Refer ZFDA Guidelines on Summary of Products Characteristics for guidance on preparation of SmPC (Part IV)* **guideline number: ZFDA.....**

1.4.2 Container labelling

Product should be labeled as prescribed in the *ZFDA Guidelines on container labeling for guidance on preparation of product labeling(Part V)* **Guideline number: ZFDA.....**

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 labeling should be clearly expressed in English and or/Swahili.

Refer ZFDA Guidelines on PIL for guidance on preparation of PIL (PartVI) . **guideline number: ZFDA.....**

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 the ZFDA, 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 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 additionally 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 declaration form is provided as **Annex III.**

1.6 Certificates of Suitability of monographs of the European pharmacopoeia (CEP) or ZFDA -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 ZFDA-APIMF* as appropriate from API manufacturer. These letters should be included in Module 1.7. (Refer **Annex IV and Annex V**)

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 ZFDA GMP guidelines. Attach a WHO-type certificate of GMP. For more information on GMP requirements and application for GMP inspection, refer *ZFDA Guidelines on Good Manufacturing Practice for more guidance.*

If available at the time of submission of application, GMP certificates for ZFDA and/or SDRA or an evidence for application for GMP inspection should be submitted in module 1.8.

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 EAC Partner States

Provide registration status of the medicinal product applied for registration in the EAC region 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 in the EAC Partner States

Applicant must declare whether a marketing application for the medicine has been rejected prior to submission of the application in EAC. If the medicine has been rejected, repeatedly deferred, withdrawn or suspended then reasons must be stated. If rejection occurs during the EAC evaluation process, ZFDA should be informed.

1.10 Evidence of API and/or FPP prequalified by WHO

If an 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 in Zanzibar except in situations where there is space is a 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 VI** *following the guidance below.*

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 3.2.P.1 should be provided.
Composition from 3.2.P.1 should be provided.

2.3. P.2 Pharmaceutical Development

A discussion of the information and data from 3.2.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 3.2.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 3.2.P.3.3.
A brief description of the process validation and/or evaluation, as described in 3.2.P.3.5.

2.3. P.4 Control of Excipients

A brief summary on the quality of excipients, as described in 3.2.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 3.2.P.5.1 should be provided.*

A tabulated summary of the batch analyses provided under 3.2.P.5.4, with graphical representation where appropriate should be included.

2.3. P.6 Reference Standards or Materials

Information from 3.2.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 3.2.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 3.2.P.8.3, with graphical representation where appropriate, should be included.
The post-approval stability protocol, as described in 3.2.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 literature 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: Efficacy for guidance on the content of this section.
The following order is recommended:

2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods: Generic applications

The objective of CTD Module 2.7.1 is to summarize all relevant information in the product dossier with regard to bioequivalence studies and/or comparative dissolution and associated analytical methods.

Annex I of the ZFDA Guideline on the Bioequivalence studies: Presentation of Biopharmaceutical and Bio-analytical Data contains a set of template tables to assist applicants in the preparation of Module 2.7.1 with regard to data to be presented. Furthermore, it is anticipated that a standardized presentation will facilitate the evaluation process.

*Refer the ZFDA Guideline on Therapeutic Equivalence Requirements: Presentation of Biopharmaceutical and Bio-analytical Data for more guidance. (**Annex V**).*

2.7.2 Summary of Clinical Pharmacology Studies

*Refer the ZFDA Guideline on Therapeutic equivalence requirements: Presentation of Biopharmaceutical and Bio-analytical Data for more guidance. (**Annex V**).*

2.7.3 Summary of Clinical Efficacy

*Refer the ZFDA Guideline on Therapeutic equivalence requirements: Presentation of Biopharmaceutical and Bio-analytical Data for more guidance. (**Annex V**).*

2.7.4 Summary of Clinical Safety

*Refer the ZFDA Guideline on Therapeutic equivalence requirements: Presentation of Biopharmaceutical and Bio-analytical Data for more guidance. (**Annex V**).*

2.7.5 Literature References

2.7.6 Synopses of Individual Studies

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 *ZFDA* 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: *ZFDA* Active Pharmaceutical Ingredient Master File (*ZFDA* -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 IV).** Letter of access should be included in Module 1.7.

Where reference is made to *ZFDA* -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 ZFDA. Applicant should provide the *Letter of Access to ZFDA -APIMF,* as appropriate from API manufacturer **(**Refer **Annex V).** 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 *ZFDA* 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.

a) 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 ZFDA who refers to the CEP.

In addition, a written commitment should be included that the applicant will inform ZFDA 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.5Reference *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.

b) 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.

c) Option 3: ZFDA **Active Pharmaceutical Ingredient Master File (***ZFDA* **-APIMF)**

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 ZFDA 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.

d) 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:

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

* 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.
Elucidation of structure

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 pharmacopoeial 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-pharmacopoeial 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 s*tandard* 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, 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), 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 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 pharmacopoeial source (BP, JP, Ph.Eur, Ph.Int, USP) where one exists and the lot number should be provided. Primary reference standards from officially recognized pharmacopoeial 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 ZFDA Guidelines on Stability Requirements for Testing Active Pharmaceutical Ingredients (APIs) and Finished Pharmaceutical Products (FPPs) (Part II) guideline number: ZFDA……

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 VII)**

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 VII).**

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 EAC 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:

- *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 ICHQ3B, ICHQ3C, ICHQ6A for more guidance.

3.2.P.5.2 Analytical procedures

The analytical procedures used for testing the FPP should be provided. Copies of the in-house analytical procedures used during pharmaceutical development (if used to generate testing results provided in the PD) as well as those proposed for routine testing should be provided. Unless modified, it is not necessary to provide copies of officially recognized compendial analytical procedures.

Refer to ICH Q2 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 ZFDA Guidelines on Stability Requirements for Testing Active Pharmaceutical Ingredients (APIs) and Finished Pharmaceutical Products (FPPs) (Part II) (guideline number: ZFDA……

3.2. REGIONAL INFORMATION

3.2.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 an agreed format for the organization of the nonclinical reports in the Common Technical Document for applications that will be submitted to ZFDA.
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 guideline which may be used for populating this format.

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

Refer 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.

Refer 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.

Refer 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.

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

4.2.2 Pharmacokinetics

4.2.2.1 Analytical Methods and Validation Reports (if separate reports are available)
4.2.2.2 Absorption
4.2.2.3 Distribution
4.2.2.4 Metabolism
4 2.2.5 Excretion
4.2.2.6 Pharmacokinetic Drug Interactions (nonclinical)
4.2.2.7 Other Pharmacokinetic Studies

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

Refer ICH Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies (S3A) for guidance on developing test strategies in toxicokinetics 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.

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 toxicokinetics evaluations)

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

Refer 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.

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

4.2.3.4 Carcinogenicity (including supportive toxicokinetics evaluations)

Refer 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.

4.2.3.4.1 Long-term studies (in order by species; including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
4.2.3.4.2 Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
4.2.3.4.3 Other studies

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

Refer 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.

4.2.3.5.1 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.

4.2.3.6 Local Tolerance

Refer 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 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

4.2.3.7.7.1 Photosafety evaluation

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

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.

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 product

Refer ZFDA Guidelines on Therapeutic Equivalence Requirements. (Part III) **Guideline number: ZFDA.....**
Refer ZFDA Guidelines on Therapeutic Equivalence Requirement. (Part III) **Guideline number: ZFDA.....**
5.3.1.3 *In vitro-In vivo* Correlation Study Reports

For Generic product

Refer ZFDA Guidelines on Therapeutic Equivalence Requirements. (Part III) **Guideline number: ZFDA.....**

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

For Generic product

Refer ZFDA Guidelines on Therapeutic Equivalence Requirements. (Part III) **Guideline number: ZFDA.....**

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 ZFDA Guidelines on Therapeutic Equivalence Requirements and bio-wavers (Part III) **Guideline number: ZFDA……**

5.4 Literature References

Refer list of the ICH guidelines on clinical studies

Annex I – Cover Letter

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

<Applicant's reference> <Date>

<ZFDA>
<Address>
<Address>
<Post code><Town>
<Country>

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 FORM FOR REGISTRATION OF PHARMACEUTICALS

(Made under section No.53 of the Act No.2/2006)

{For official use only} Date…….. Application No…… ……

PRODUCT PARTICULARS

1. Proprietary name
1.1 Name of the active ingredient(s) (International Non-proprietary Name in English)
1.2 Pharmacotherapeutic classification (Anatomic-Therapeutic Classification system)
2. Pharmaceutical Dosage form
2.1 Route of administration
2.2 Container, closure and administration devices
2.3 Package sizes…….. 2.4 Shelf life…… 2.5 Shelf life (after first opening of container) …….. 2.6 Shelf life (after reconstitution)…… 2.7 Storage conditions……..
2.8 Narcotic or Psychotropic Prescription only Pharmacy only General sale (OTC) Other information

3. Details of applicant (who must be the future holder of the marketing authorization/registration certificate)

Name: ……..

Business Address: ……..

Postal Address: ……..

Country: ……..

Phone: Fax: Email:

3.1 Details of a locally responsible person (who must be nominated by the applicant and submit evidence of power of attorney)

Name: ……

Business Address: ……

Country: ……

Phone: Fax: Email: -

3.2 Manufacturer(s), site(s) and authorized person(s) for the pharmaceutical dosage form

NAME (Attach WHO Certification of each)	ACTIVITY	SITE (Business Address, Phone and Country)	AUTHORIZED PERSON
			Name: Business Address:

Source (manufacturer) of Active Pharmaceutical Ingredient(s):

Name: ……

Street Address: ……

Business Address: ……

Country: ……

Phone: Fax: Email:

4. Status of marketing authorization/registration in the country of origin and authorization/registration number and date where applicable -

5. Registration status for this medicine in the SADC member states and in other countries

Registered:	Country: Date of authorization: Authorization number: Trade name:
Pending:	Country: Date of submission: Application number:
Rejected:	Country: Date of rejection: Application number: Reason for rejection:
Withdrawn (by applicant before registration)	Country: Date of withdrawal: Reason for withdrawal: Trade name:
Withdrawn (by applicant after registration)	Country: Date of withdrawal: Reason for withdrawal: Trade name:
Suspended/Revoked/Withdrawn (by competent authority)	Country: Date of withdrawal: Reason for withdrawal: Trade name:

6. Proposed indications of the product

P.O.Box 3595, Mombasa Area, Changu Road, Zanzibar
Tel: + 255 24 2233959-, Fax:+ 255 24 2233959, Website www.zfda.go.tz, E mail: info@zfda.go.tz

7. Complete composition per dosage unit

Name (INN) of	Reason for inclusion	Quantity	Unit of measure	Referenced monograph
- API				
1.				
2., etc.				
- Excipients				
1.				
2., etc. -				

8. Declaration by an applicant

I, the undersigned certify that all the information in this form and all accompanying documentation is correct. I further certify that I have examined the following statements and I attest to their correctness: 1. The current edition of the WHO guideline on **"Good Manufacturing Practice for Pharmaceutical Products"**, and/or equivalent national guideline, is applied in full in all premises involved in the manufacture of this medicine.

2. The formulation per dosage form correlates with the master formula and with the batch manufacturing record.

3. The manufacturing procedure is exactly as specified in the master formula and batch manufacturing record.

4. Each batch of all starting materials is either tested or certified (in accompanying certificate of analysis for that batch) against the full specifications in the accompanying documentation and must comply fully with those specifications before it is released for manufacturing purposes.

5. All batches of the active pharmaceutical ingredient(s) are obtained from the source(s) specified in the accompanying documentation.

6. No batch of active pharmaceutical ingredient(s) will be used unless a copy of the batch certificate established by the manufacturer is available.

7. Each batch of the container/closure system is tested or certified against the full specifications in the accompanying documentation and complies fully with those specifications before released for the manufacturing purposes.

8. Each batch of the finished product is either tested, or certified (in an accompanying certificate of analysis for that batch), against the full specifications in the accompanying documentation and complies fully with release specifications before released for sale.

9. The person releasing the product is an authorized person as defined by the WHO guideline **"Good Manufacturing Practices: Authorized person - the role, functions and training"** and/or an equivalent Tanzania guideline.

10. The procedures for control of the finished product have been validated for this information. The assay method has been validated for accuracy, precision, specificity and linearity.

11. All the documentation referred to in this certificate is available for review during GMP inspection.

12. Clinical Trials were conducted in accordance with Good Clinical Practice, where applicable. -
I also agree that:

1. The holder of marketing authorization/registration certificate is obliged to follow Zanzibar Food, Drugs & Cosmetics Board requirements for handling adverse reactions of its products.

2. The holder of registration certificate is obliged to follow Zanzibar Food, Drugs & Cosmetics Board requirements for handling batch recalls of its products.

Name:……

Qualification:……

Position in the company:……

Signature:……

Date:…… **Official stamp:** -

N.B. False declaration constitutes an offence

P.O.Box 3595, Mombasa Area, Changu Road, Zanzibar
Tel: + 255 24 2233959-, Fax:+ 255 24 2233959, Website www.zfda.go.tz, E mail: info@zfda.go.tz

APPLICATION FORM FOR REGISTRATION OF PHARMACEUTICALS

(Made under section No.53 of the Act No.2/2006)

v

FOR OFFICIAL USE ONLY

Fees ……..... Receipt No. ……. ……of ……,

License granted/not granted because ……

…… License No. ……..

…… ……

Date **Responsible Registration Officer Signature**

Approved by Management meeting No. …… ..... of ……..

…….. **……**

Date **Signature for Executive Director and stamp**

P.O.Box 3595, Mombasa Area, Changu Road, Zanzibar
Tel: + 255 24 2233959-, Fax:+ 255 24 2233959, Website www.zfda.go.tz, E mail: info@zfda.go.tz

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.

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

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

.....
.....
.....
.....

Annex IV: Letter of Access to CEP

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

<Applicant's reference> <Date>

<Zanzibar Food and Drug Agency>
<Address>
<Address>
<Post code><Town>
<Country>

Dear Sir/Madam,

Subject: Authorization to access Certificate of Suitability (CEP)

Reference is made to the above subject matter.

Consent is hereby granted to *ZFDA* 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 ZFDA 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 ZFDA 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 ZFDA 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 Zanzibar before written approval is granted by the ZFDA.

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 *ZFDA* evaluation of this CEP should be forwarded to:

(*Name and address*)

Yours faithfully

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

Annex V: Letter of Access to APIMF

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

<Applicant's reference> <Date>

<Zanzibar Food and Drug Agency>
<Address>
<Address>
<Post code><Town>
<Country>

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 *ZFDA* 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 ZFDA 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 ZFDA 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 ZFDA 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 ZFDA 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 Zanzibar before written approval is granted by the ZFDA.

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 ZFDA is authorized to request and refer to the evaluation reports of these agencies. ZFDA is also authorized to exchange its own evaluation reports with these and other regulatory authorities.

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

{Name and address}

Yours faithfully

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

Annex VI: 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 activ 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 ZFDA 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 ZFDA 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:

Name and address (including block(s)/unit(s))	**Responsibility**	**APIMF/CEP number (applicable)**

(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**

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 ioavailability or biowaiver, stability batches):

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 closur system**	**Completed (and proposed) testing intervals**

Storage condition (◦C, % RH)	Batch number	Batch size	Container closur system	Completed (and proposed) testing 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 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.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. p unit	%	Quant. p unit	%	Quantity per unit	%
<complete with appropriate title e.g. Core tablet, Contents of capsule, Powder f 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 an quality standar (e.g. NF, BP, Ph.Eur, in-house)	**Relevant batches**							
	Comparative bioavailability or biowaiver		**Stability**		**Process validation**		**Commercial (2.3.P.1)**	
	<Batch nos. ar sizes>		**<Batch nos. ar sizes>**		**<Batch nos. ar sizes>**		**<Batch nos. ar sizes>**	
	Theor. quantity per batch	**%**	**Theor. quantity pe 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:

2.3.P.2.2.3 Physicochemical and Biological Properties

(a) Discussion of the parameters relevant to the performance of the FPP (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

For excipient(s) used for the first time in FPP or by a new route of administration, full details of manufacture, characterization and controls, with cross references to supportingsafetydata(nonclinicaland/orclinical),shouldbeprovidedaccordingtothe 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

(a) Description of the batches:

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

(b) 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.				

(c) 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 Threshol	
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 condition (◦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 eac 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	
	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

(a) 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

ANALYTICAL PROCEDURES AND VALIDATION INFORMATION SUMMARIES

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):			

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) :				

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 VII: 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:

1. A review of starting and primary packaging materials used in the FPP, especially those from new sources.
2. A tabulated review and statistical analysis of quality control and in-process control results.
3. A review of all batches that failed to meet established specification(s).
4. A review of all critical deviations or non-conformances and related investigations.
5. A review of all changes carried out to the processes or analytical methods.
6. A review of the results of the stability-monitoring programme.
7. A review of all quality-related returns, complaints and recalls, including export-only medicinal products.
8. A review of the adequacy of previous corrective actions.
9. 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:

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

Abbreviations and Acronyms

APIs:	Active Pharmaceutical Ingredient
EAC:	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
ZFDA	Zanzibar Food and Drug Agency

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 adapted from WHO Technical Report Series, No. 953, Annex II. Further guidance can be found in *International Council 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. GUIDELINE

2.1 Active pharmaceutical ingredient

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 (**Annex I**).

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, 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 EAC countries are either $30^0C \pm 2\ ^0C/65\% \pm 5\%$ RH or $30 \pm 2^0C/75\% \pm 5\%$ RH. Alternative conditions should be

supported with appropriate evidence, which may include literature references or in-house studies, demonstrating that storage at 30^{0}C 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 6 months 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:-

1. 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.

2. 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.

3. 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:

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

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

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

4. 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.

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:

1. Number of batch(es) per strength and different batch sizes, if applicable.
2. The batch size should be recorded, if different batch sizes are employed;
3. Relevant physical, chemical, microbiological and biological test
4. Methods;
5. Acceptance criteria;
6. Reference to test methods;
7. Description of the container closure system(s);
8. Testing frequency;
9. 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
10. 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.

3. 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:-

1. 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.)

2. Any degradation product exceeding its acceptance criterion.

1. 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.

4. Failure to meet the acceptance criterion for pH.

Or

5. 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.

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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).
   - International Conference on Harmonisation. *ICH Q1E: Evaluation for stability data* (http://www.ich.org/LOB/media/MEDIA415.pdf).
   - International Conference on Harmonisation. *ICH Q2R1*)*: Validation ofanalytical procedures: text and methodology* (http://www.ich.org/LOB/media/MEDIA417.pdf).
   - International Conference on Harmonisation. *ICH Q3A: Impurities in new drug substances* (http://www.ich.org/LOB/media/MEDIA422.pdf).
   - International Conference on Harmonisation. *ICH Q3B: Impurities in new drug products* (http://www.ich.org/LOB/media/MEDIA421.pdf).
   - International Conference on Harmonisation. *ICH Q5C: Stability testing of biotechnological/ biological products* (http://www.ich.org/LOB/media/MEDIA427.pdf).
   - International Conference on Harmonisation. *ICH Q6A: Specifications: Testprocedures and acceptance criteria for new drug substances and new drug products: Chemical substances* (http://www.ich.org/LOB/media/MEDIA430.pdf).
   - International Conference on Harmonisation. ICH Q6B: *Specifications: Testprocedures and acceptance criteria for biotechnological/ biological products*(http://www.ich.org/LOB/media/MEDIA432.pdf).
   - Further information can be found on the ICH homepage:http://www.ich.org/cache/compo/276-254-1.html.

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10. Guidelines for registration of fi xed-dose combination medicinal products. Appendix 3: Pharmaceutical development (or pre-formulation) studies. Table A1: Typical stress conditions in preformulation stability studies. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth report. Geneva, World Health Organization, 2005, Annex 5 (WHO Technical Report Series, No. 929).

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14. *Prequalification Programme – Priority Essential Medicines. A United Nations Programme managed by WHO. Information for applicants* (http://mednet3.who.int/prequal/).

15. *ASEAN Guideline on stability study of drug product*, 9th ACCSQ-PPWG Meeting, Philippines, 21–24 February 2005, version 22 February 2005.

Annex 1

Examples of testing parameters

Section I for active pharmaceutical ingredients

In general, appearance, assay and degradation products should be evaluated for all active pharmaceutical ingredients (APIs). Other API parameters that may be susceptible to change should also be studied where applicable.

Section II for finished medicinal products

The following list of parameters for each dosage form is presented as a guide to the types of tests to be included in a stability study. In general, appearance, assay and degradation products should be evaluated for all dosage forms, as well as the preservative and antioxidant content if applicable. The microbial quality of multiple-dose sterile and non-sterile dosage forms should be controlled. Challenge tests should be carried out at least at the beginning and at the end of the shelf-life. Such tests would normally be performed as part of the development programme, for example, within primary stability studies. They need not be repeated for subsequent stability studies unless a change has been made which has a potential impact on microbiological status. It is not expected that every test listed be performed at each time point. This applies in particular to sterility testing, which may be conducted for most sterile products at the beginning and at the end of the stability test period. Tests for pyrogens and bacterial endotoxins may be limited to the time of release.

Sterile dosage forms containing dry materials (powder filled or lyophilized products) and solutions packaged in sealed glass ampoules may need no additional microbiological testing beyond the initial time point. The level of microbiological contamination in liquids packed in glass containers with flexible seals or in plastic containers should be tested no less than at the beginning and at the end of the stability test period; if the long-term data provided to the regulatory authorities for marketing authorization registration do not cover the full shelf-life period, the level of microbial contamination at the last time point should also be provided.

The list of tests presented for each dosage form is not intended to be exhaustive, nor is it expected that every test listed be included in the design of a stability protocol for a particular finished medicinal product (FPP) (for example, a test for odour should be performed only when necessary and with consideration for the analyst's safety). The storage orientation of the product, i.e. upright versus inverted, may need to be included in a protocol when 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.

Tablets

Dissolution (or disintegration, if justified), water content and hardness/ friability.

Capsules

- Hard gelatin capsules: brittleness, dissolution (or disintegration, if justified), water content and level of microbial contamination.
- Soft gelatin capsules: dissolution (or disintegration, if justified), level of microbial contamination, pH, leakage, and pellicle formation.

Oral solutions, suspensions and emulsions

Formation of precipitate, clarity (for solutions), pH, viscosity, extractables, level of microbial contamination. Additionally for suspensions, dispersibility, rheological properties, mean size and distribution of particles should be considered. Also polymorphic conversion may be examined, if applicable.
Additionally for emulsions, phase separation, mean size and distribution of dispersed globules should be evaluated.

Powders and granules for oral solution or suspension

Water content and reconstitution time. Reconstituted products (solutions and suspensions) should be evaluated as described above under "Oral solutions suspensions and emulsions", after preparation according to the recommended labelling, through the maximum intended use period.

Metered-dose inhalers and nasal aerosols

Dose content uniformity, labelled number of medication actuations per container meeting dose content uniformity, aerodynamic particle size distribution, microscopic evaluation, water content, leak rate, level of microbial contamination, valve delivery (shot weight), extractables/ leachables from plastic and elastomeric components, weight loss, pump delivery, foreign particulate matter and extractables/leachables from plastic and elastomeric components of the container, closure and pump. Samples should be stored in upright and inverted/on-the-side orientations.

For suspension-type aerosols, microscopic examination of appearance of the valve components and container's contents for large particles, changes in morphology of the API particles, extent of agglomerates, crystal growth, foreign particulate matter, corrosion of the inside of the container or deterioration of the gaskets.

Nasal sprays: solutions and suspensions

Clarity (for solution), level of microbial contamination, pH, particulate matter, unit spray medication content uniformity, number of actuations meeting unit spray content uniformity per container, droplet and/ or particle size distribution, weight loss, pump delivery, microscopic evaluation (for suspensions), foreign particulate matter and extractables/leachables from plastic and elastomeric components of the container, closure and pump.

Topical, ophthalmic and otic preparations

Included in this broad category are ointments, creams, lotions, paste, gel, solutions, eye drops and cutaneous sprays.

i. Topical preparations should be evaluated for clarity, homogeneity, pH, suspendability (for lotions), consistency, viscosity, particle size distribution (for suspensions, when feasible), level of microbial contamination/sterility and weight loss (when appropriate).

ii. Evaluation of ophthalmic or otic products (e.g. creams, ointments, solutions and suspensions) should include the following additional attributes: sterility, particulate matter and extractable volume.

iii. Evaluation of cutaneous sprays should include: pressure, weight loss, net weight dispensed, delivery rate, level of microbial contamination, spraypattern, water content and particle size distribution (for suspensions).

Suppositories

Softening range, disintegration and dissolution (at 37 °C).

Small volume parenterals (SVPs)

Colour, clarity (for solutions), particulate matter, pH, sterility, endotoxins.

Stability studies for powders for injection solution should include monitoring for colour, reconstitution time and water content. Specific parameters to be examined at appropriate intervals throughout the maximum intended use period of the reconstituted drug product, stored under condition(s) recommended on the label, should include clarity, colour, pH, sterility, pyrogen/endotoxin and particulate matter. It may be appropriate to consider monitoring of sterility after reconstitution into a product, e.g. dual-chamber syringe, where it is claimed that reconstitution can be performed without compromising sterility.

i. The stability studies for Suspension for injection should include, in addition, particle size distribution, dispersibility and rheological properties.

ii. The stability studies for Emulsion for injection should include, in addition, phase separation, viscosity, mean size and distribution of dispersed phase globules.

Large volume parenterals (LVPs)

Colour, clarity, particulate matter, pH, sterility, pyrogen/endotoxin and volume.

Transdermal patches

In vitro release rates, leakage, level of microbial contamination/sterility, peel and adhesive forces.

Annex 2

Recommended labelling statements

1. Active pharmaceutical ingredients

The statements that should be used if supported by the stability studies for active pharmaceutical ingredients (APIs) are listed in Table 1.

Table 1

Recommended labelling statements for active pharmaceutical ingredients (APIs)

Testing condition under which the stability of the API has been demonstrated	**Recommended labelling statement**
30°C/65% RH (long-term) 40°C/75% RH (accelerated)	"Do not store above 30°C"*
30°C/75% RH (long-term) 40°C/75% RH (accelerated)	"Do not store above 30°C"
5°C ± 3 °C	"Store in a refrigerator (2°C to 8°C)"
-20°C± 5°C	"Store in freezer"

* "Protect from moisture" should be added as applicable.

Finished pharmaceutical products

The statements that should be used if supported by the stability studies for finished pharmaceutical products (FPPs) are listed in Table 2.

Table 2

Recommended labelling statements for finished pharmaceutical products (FPPs)

Testing condition under which the stability of the API has been demonstrated	**Recommended labelling statement**
30°C/65% RH (long-term) 40°C/75% RH (accelerated)	"Do not store above 30°C"*
30°C/75% RH (long-term) 40°C/75% RH (accelerated)	"Do not store above 30°C"
5°C ± 3 °C	"Store in a refrigerator (2°C to 8°C)"
-20°C ± 5°C	"Store in freezer"

* "Protect from moisture" should be added as applicable.

PART III:
ZFDA GUIDELINES ON THERAPEUTIC EQUIVALENCE

ABBREVIATIONS AND ACRONYMS

APIs	-	Active Pharmaceutical Ingredients
BCS	-	Biopharmaceutics Classification System
BMGF	-	Bill and Melinda Gates Foundation
BMR	-	Batch Manufacturing Record
CoA	-	Certificate of Analysis
EAC	-	East African Community
EAC-MRH	-	East African Community Medicines Regulatory
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
MER	-	Medicines Evaluation and Registration
NEPAD	-	New Partnership for African Development
NMRA	-	National Medicines Regulatory Authority
pKa	–	Dissociation constant
SD	-	Standard deviation
TWG	-	Technical Working Group
USFDA	–	United States Food and Drug Administration
WHO	-	World Health Organization

$Ae_{(0-t)}$	Cumulative urinary excretion of unchanged drug from administration until time t;
$AUC_{(0-t)}$:	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;
$AUC_{(0-\tau)}$:	AUC during a dosage interval at steady state;
$AUC_{(0-72h)}$	Area under the plasma concentration curve from administration to 72h;
C_{max}:	Maximum plasma concentration;
$C_{max,ss}$:	Maximum plasma concentration at steady state;
residual area	Extrapolated area ($AUC_{(0-\infty)}$ - $AUC_{(0-t)}$)/ $AUC_{(0-\infty)}$;
R_{max}	Maximal rate of urinary excretion;
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;
λ_z:	Terminal rate constant;
SmPC	Summary of Product Characteristics

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 bioavailabilities 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 safetycan 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 bio waivers 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 hospitalization or prolongation of existing hospitalization, 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/milliliter (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 Zanzibar. If not currently approved in Zanzibar, 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 homogenous 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 guidelines.

1.0 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 bioavailabilities (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, 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 (Pharmaceutical Development).

2.0 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.

Exemptions for carrying out bioequivalence studies

Omission of BE studies must be justified except if a product fulfills 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;

n) Gases;

3.0 MAIN GUIDLEINE TEXT

3.1 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. 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-WHO 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 randomized, 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 randomized 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)

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 comparator product in the bioequivalence study should meet the criteria stipulated

in Annex IV.

In an application for extension of a medicinal product which has been initially approved by ZFDA 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 Comparator product batch for the bioequivalence study. (to be removed and moved to 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 a Competent Authority'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 pre-requisite 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 should be collected. 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 (C_{max}, t_{max}) 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

Also 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 compound. 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 drug 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 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 characterized, 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 evaluable data for both of the test and comparator products (or who fail to provide evaluable 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 randomized 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:-

1) 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.

2) 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, $AUC_{(0-t)}$ 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 bioinequivalence 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 analyzing 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. For a list 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 C_{max} 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 C_{max} 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 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·s_{WR}], 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 s_{WR} is the within-subject standard deviation of the log-transformed values of C_{max} 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

$$CV(\%) = 100\sqrt{e^{s_{WR}^2} - 1}$$

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 (annexe I) including basic requirements 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 I) 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) or Bioequivalence Trial Information (BTIF) Annex V) 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. Audits 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 selection of comparator products (Annex IV) to be used in establishing inter changeability. 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 III.

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 I).

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 that 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.

4 OTHER APPROACHES TO ASSESS THERAPEUTIC EQUIVALENCE

4.1 Comparative pharmacodynamics studies

Studies in healthy volunteers or patients using pharmacodynamics measurements may be used for establishing equivalence between two pharmaceuticals 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.

4.2 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.

4.3 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 modified release product and the conventional release product when used as 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.

i. 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.

ii. 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.

iii. 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.

iv. 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, C_{max} and C_{min} determined using log – transformed data should generally be within the range 80 to 125% when the formulation are compared at steady state.
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.

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.

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.

Annex I: 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 reference 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 Annex III)
- To investigate batch to batch consistency of the products (test and reference) 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. biorelevance) 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 $f2$ 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 $f2$ 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 II: Bioequivalence study requirements for different dosage forms

Although this guideline concerns immediate release formulations, Annex II 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 reference medicinal product, bioequivalence should be demonstrated in *in vivo* bioequivalence studies. However, when the active substance in both test and reference products is identical (or contain salts with similar properties as defined in Annex III, Section III), *in vivo* bioequivalence studies may in some situations not be required as described below and in Annex III.

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 III). 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 III). 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 reference 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 reference medicinal product, the following recommendations regarding study design apply:-

- if the reference 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 reference 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 reference 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 reference 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 III: 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 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 reference 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 I) 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 reference 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 reference 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.

Biowaiver Application Form: Biopharmaceutics Classification System (BCS)

This application form is designed to facilitate information exchange between the Applicant and ZFDA if the Applicant seeks to waive bioequivalence studies based on the Biopharmaceutics Classification System (BCS). For further information, please study the respective–ZFDA 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.

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) ZFDA.

The signed paper version of this Biowaiver Application Form together with Annexes (and their electronic copies on CD-ROM) should be included to the bioequivalence part of the submitted dossier and sent by surface mail to the following address:

Executive Director,
Zanzibar Food and Drug Agency,
P.O BOX 3595,
Zanzibar.
Tanzania.

Administrative data

1. INN of active ingredient(s)
<< *Please enter information here* >>

2. Dosage form and strength
<< *Please enter information here* >>

3. Product ZFDA Reference number *(if product dossier has been accepted 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)

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 >>

1.0 COMMENTS FROM REVIEW OF SECTION 1 –*OFFICIAL USE ONLY*

2. Solubility

(Completion of this section is not necessary if the API(s) are included on the list of biowaiver-eligible APIs in the PQTm document *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 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3	Experiment 1 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 >>

2.0 COMMENTS FROM REVIEW OF SECTION 2 –*OFFICIAL USE ONLY*

Annex IV: 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. interchange ability) of their product to an existing medicinal product(s).

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 in the ZFDA guidelines on therapeutic equivalence requirements,

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]

The applicant has the following options which are listed in order of preference:-

1. To choose an innovator product;

2. To choose a product which is approved and has been on the market in any of the ICH and associated countries for more than five years;

3. To choose the WHO recommended comparator product (as presented in the developed lists);

In case no recommended comparator product is identified; or in case recommended comparator product cannot be located in a well regulated market with stringent regulatory authority as noted above, the applicant should consult ZFDA 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 Council 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.

---

[11] Countries officially participating in ICH are the ICH members European Union, Japan and USA; and the ICH observers Canada and Switzerland.

ANNEX V: Bioequivalence Trial Information (BTIF)

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 ZFDA Official 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 ZFDA

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 ZFDA together with the bioequivalence part of the dossier to the address below

Executive Director,
Zanzibar Food and Drug Agency,
P.O BOX 3595,
Zanzibar.
Tanzania.

BIOEQUIVALENCE PART OF A NEW DOSSIER

Reference of the session		
Date		
Type of product		
Type of dossier	**EFFICACY**	
Type of submission	**NEW**	
First assessor	Name	Signature
Second assessor	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		
Date of the submission		
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 Organisation(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 from different countries excluding whenever possible evaluators from the country of manufacturer/applicant responsible for assessing product quality including pharmaceutical and analytical aspects.

The assessment report should be typed with “Bookman Old Style 12” fonts. The format of tables must not be changed.

BIOEQUIVALENCE TRIAL INFORMATION

1.0 SUMMARY OF BIOAVAILABILITY/BIOEQUIVALENCE STUDIES PERFORMED

(Provide a brief description of each comparative bioavailability study included in the submission)

*…

2.0 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 each product strength 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)*

*…

Component and Quality Standard	Function	Strength (label claim)			
		XX mg		XX mg	
		Quantity per unit	%*	Quantity per unit	%*
TOTAL					

**each ingredient expressed as a percentage of the total core or coating weight*

Composition of the batches used for clinical, bioequivalence or dissolution studies				
Batch number				
Batch size (number of unit doses)[1]				
Comments, if any				
Comparison of unit dose compositions and of clinical FPP batches (duplicate this table for each strength, if compositions are different)				
Ingredients	Unit dose (mg)	Unit dose (%)	Biobatch (kg)	Biobatch (%)
Equivalence of the compositions or justified differences				

[1] 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.

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.

3.0 CLINICAL STUDY REPORT

Study #:

Study Title:

Location of Study Protocol:

Start and stop dates for each phase of the clinical study:

*…

3.1 ETHICS

(a) Name of review committee, date of approval of protocol and consent form, location of approval letter in the submission

*…

(b) State location of a reference copy of the informed consent form

*…

3.2 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)*

*…

3.3 STUDY OBJECTIVES

Briefly state the study objectives.

*…

3.4 INVESTIGATIONAL PLAN

3.4.1 Overall Study Design and Plan – Description

(Describe the type of study design employed in 1-2 sentences)

*…

3.4.2 Selection of Study Population

*…

3.4.2.1 Inclusion Criteria

*…

3.4.2.2 Exclusion Criteria

(List the exclusion criteria applied to subjects)

*…

3.4.2.3 Removal of Trial subjects from Trial or Assessment

*…

(a) Number of subjects enrolled in the study

(All subjects including alternates, withdrawals, and dropouts)

*…

(b) Withdrawals

(Identify each withdrawal by subject and provide the reason for withdrawal and at what point in the study the withdrawal occurred)

*…

3.4.2.4 Health Verification

(Individual data should be 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)

*…

3.4.3 Products Administered

3.4.3.1 Test Product

*…

(a) Batch number, size and date of manufacture 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)

*…

3.4.3.2 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 reference product

*…

(b) Batch number and expiry date for the reference product

*…

(c) Purchase, shipment, storage of the reference product

(This information should be cross-referenced to location in submission of documents (e.g. receipts) proving conditions)

*…

(d) Potency (measured content) of the reference 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)

*…

(e) Justification of choice of reference product

(Provide short summary here and cross-reference to location of comprehensive justification in study protocol)

*…

3.4.4 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)

*…

3.4.5 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

*…

3.4.6 Blinding

3.4.6.1 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:_____

*…

3.4.6.2 Identify ZFDA held the study code and when the code was broken

*…

3.4.7 Drug Concentration Measurements

*…

3.4.7.1 Biological fluid(s) sampled

*…

3.4.7.2 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)

*…

3.4.7.3 Sample Handling

*…

(a) Describe the method of sample collection

*…

(b) Describe sample handling and storage procedures

*…

3.5 COMMENTS FROM REVIEW OF SECTION 3.0 –*FOR OFFICIAL USE ONLY*

4.0 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 Number of smokers included in the study

*…

(a) Indicate how many cigarettes smoked per day per subject

*…

(b) Comment on the impact on study

*…

4.3 COMMENTS FROM REVIEW OF SECTION 4.0 – *FOR OFFICIAL USE ONLY*

5.0 PROTOCOL DEVIATIONS

5.1 Protocol deviations during the clinical study

(Describe any such deviations and discuss their implications with respect to bioequivalence)

*…

5.2 COMMENTS FROM REVIEW OF SECTION 5.0 *FOR OFFICIAL USE ONLY*

6.0 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)

*…

6.2 COMMENTS FROM REVIEW OF SECTION 6.0 –*FOR OFFICIAL USE ONLY*

7.0 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

	Test			Reference		
Parameter	Arithmetic Mean	Standard deviation	Interindividual coefficient of variation (%)	Arithmetic Mean	Standard deviation	Interindividual coefficient of variation (%)
AUC_T (units)						
AUC_I (units)						
C_{max} (units)						
T_{max} (units)						
$T_{½}$ (units)						

(State method of AUC calculation and method of extrapolation. Indicate location of description in protocol)

*…

(b) Ratio of AUC_T to AUC_I

(State mean ratio for both test and reference, state location in submission where individual ratios can be found,)

*…

7.3 Statistical Analysis

(Provide the following results from the ANOVA (parametric) on the logarithmically transformed AUC_T and C_{MAX} and other relevant parameters, e.g. in the case of steady-state designs, AUC_τ , C_{MAX} , and C_{MIN} ; state software which has been used for computing ANOVA)

*…

(a) Geometric means, Results from ANOVA, Degrees of Freedom (DF) and derived CV (intraindividual)

Parameter	Test	Reference	% Ratio of Geometric Means	90 % Confidence Interval	DF	CV (%)
AUC_T (units)						
AUC_I (units)						
C_{max} (units)						

*…

(b) Period and/or sequence effects

(State whether any period- and/or sequence-effects have been found. If yes, provide short discussion of effects here, and state location in submission where comprehensive explanation is provided)

*…

7.4 DISCUSSION OF RESULTS

(State location of the discussion of the results in the submission. If the discussion currently included in the study report does not include comparisons of results, including inter- and intraindividual variability, of this study with published results (literature, product information of reference product (innovator), such a discussion should be provided here and copies of the references used should be appended to this document)

*…

7.5 COMMENTS FROM REVIEW OF SECTION 7.0 –FOR OFFICIAL USE ONLY

8.0 ANALYTICAL STUDY REPORT

8.1 Analytical Technique

*…

8.1.1 Analytical protocol

(State the location of the analytical protocol)

*…

8.1.2 Identify analyte(s) monitored

*…

8.1.3 Comment about source and validity of reference standard

*…

8.1.4 Identify analytical technique employed

*…

8.1.5 Identify method of detection

*…

8.1.6 Identify internal standard

*…

8.1.7 If based on a published procedure, state reference citation

*…

8.1.8 Identify any deviations from protocol

*…

8.1.9 Dates of subject sample analysis

*…

8.1.10 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)

*…

8.1.11 State whether all samples for a given subject were analysed together in a single analysis run

*…

8.2 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

*…

(c) Summarize descriptive data including slope, intercept, correlation coefficients

*…

(d) Describe the regression model used including any weighting

*…

(e) State the limit of quantitation (LOQ)

(Summarize inter-day and intra-day precision and accuracy at the LOQ)

*…

8.3 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

*…

8.4 Precision and Accuracy

*…

(a) Summarize inter-day and intra-day precision and accuracy of QC samples analysed during subject sample analysis and inter-day precision of back-calculated standards

*…

8.5 Repeat Analysis

(a) List repeats by sample identification and include the following information for each repeat: initial value; reason for repeat; repeat value(s); accepted value; and reason for acceptance

*…

(b) Report the number of repeats as a percentage of the total number samples assayed

*…

8.6 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)

*…

8.7 COMMENTS FROM REVIEW OF SECTION 8.0 – FOR OFFICIAL USE ONLY

9.0 ANALYTICAL VALIDATION REPORT

9.1 Precision and Accuracy

*…

(a) Summarize inter-day and intra-day accuracy and precision during assay validation

*…

(b) Summarize inter-day and intra-day accuracy and precision during assay re-validation

(If applicable)

*…

9.2 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 autosampler storage stability

*…

(e) Summarize data from any other stability studies conducted

(e.g., stock solution stability)

*…

9.3 Specificity

(Methods to verify specificity against endogenous/exogenous compounds & results)

*…

9.4 Matrix effect (in case of MS detection)

(Methods to verify the matrix effect & results)

*…

9.5 Recovery

(Method and results of assessment for analyte and internal standard including mean and CV%)

*…

9.6 COMMENTS FROM REVIEW OF SECTION 9.0 –FOR OFFICIAL USE ONLY

10.0 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 of study sites (see 3.2 b-d)

*…

10.3 COMMENTS FROM REVIEW OF SECTION 10 –FOR OFFICIAL USE ONLY

11.0 CONCLUSIONS AND RECOMMENDATIONS – FOR OFFICIAL USE ONLY

POINTS TO BE COMMUNICATED TO THE MANUFACTURER

A. General remark, if applicable

Each application should be considered as a stand-alone submission. Observations of evaluators already clarified through correspondence with ZFDA should be adopted in the new application as amended in order to avoid wasting evaluators' time.

B. Overall conclusion

Please fill in the relevant conclusion, based on the review of the data on efficacy and safety, in the first part of the document.

Please copy all relevant information to be communicated to the manufacturer in the corresponding letter and save it accordingly.

RECOMMENDATIONS FOR INSPECTION

Annex VI: Biowaiver Application Form: Additional Strength

This application form is designed to facilitate information exchange between the Applicant and) if a biowaiver is requested for additional strength(s) of the submitted product(s). This form is not to be used, if the Applicant seeks to waive bioequivalence studies, based on the Biopharmaceutics Classification System (BCS), in which situation a separate "*Biowaiver Application Form: Biopharmaceutics Classification System (BCS)"* should be used.

For further guidance, please consult:

- ZFDA Compendium on Medicines Evaluation and Registration Part III "ZFDA *Guidelines on Therapeutic Equivalence Studies*". Available on the ZFDA website at www.zfda.go.tz.

Employing the dissolution conditions described in the guidelines referenced above, *in vitro* dissolution data comparing the different strengths of the submitted product, one of which is the reference strength, must be provided.

The format of the dissolution study report(s) provided in support of this waiver request should be consistent with the format employed as a part of a BCS-based biowaiver application.

Final assessment of the proportionality of the proposed formulations and the acceptability of the comparative dissolution data will be made during the evaluation of Quality part of the dossier.

General Instructions to complete the Application Form:

- 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 2.4 indicate in which Annex the Certificate of Analysis can be found.

- The appended electronic documents should be clearly identified in their file names, which should include the product name and Annex number.
- Please provide the application form as an MS Word file.
- 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 ZFDA.

The signed paper version of this Biowaiver Application Form together with Annexes (and their electronic copies on CD-ROM) should be included to the bioequivalence part of the submitted dossier and sent by surface mail to the following address:

Executive Director,
Zanzibar Food and Drug Agency,
P.O BOX 3595,
Zanzibar.
Tanzania.

Administrative data

1. INN of active ingredient(s)
< *Please enter information here* >
2. Dosage form and strengths
< *Please enter information here* >
3. Product EAC Reference numbers *(if available for any strengths of the product line, including the reference strength)*
< *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 biowaiver dissolution studies were conducted *(if applicable)*
< *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)

1. Test product

1.1 Tabulation of the composition of formulation proposed for marketing

- Please state the location of the master formulae in the quality part of the submission.
- For solid oral dosage forms the table should contain only the ingredients in tablet core or contents of a capsule. A copy of the table should be filled in for the film coating or hard capsule, if any.
- Biowaiver batches should be at least of pilot scale (10% of production scale or 100,000 capsules or tablets whichever is greater) and manufacturing method should be the same as for production scale.

Composition of the batch used for comparative dissolution studies				
Batch number for biowaiver batch				
Batch size (number of unit doses)				
Date of manufacture				
Expiry date				
Comments, if any				
Unit dose compositions and FPP batch composition				
Ingredients (Quality standard)	Unit dose (mg)	Unit dose (%)	Biowaiver batch (kg)	Biowaiver batch (%)

1.2 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 (CoA) in this biowaiver submission.

<< Please enter information here >>

1.3 Pharmacokinetics

- State whether the drug displays linear or non-linear pharmacokinetics
- Provide literature-based support for your response and append all references cited in the response and state the location of these references in the dossier.
- State concentrations at which non-linearity occurs and any known explanations. Particular attention should be paid to absorption and first-pass metabolism

<< Please enter information here >>

1.4 COMMENTS FROM REVIEW OF SECTION 1.1 - 1.3 –FOR OFFICIAL USE ONLY

2. Reference strength

2.1. Reference strength

In this context, the reference strength is the strength of the FPP that was compared to the EAC Comparator product in an *in vivo* bioequivalence study.

2.2. Tabulation of batch information for the reference strength

The biobatch of the reference strength (batch employed in the *in vivo* bioequivalence study) should be employed in the comparative dissolution studies.

Batch information for batch used for comparative dissolution studies				
Batch number				
Batch size (number of unit doses)				
Date of manufacture				
Expiry date				
Comments, if any				
Unit dose compositions and FPP batch composition				
Ingredients (Quality standard)	Unit dose (mg)	Unit dose (%)	Batch (kg)	Batch (%)

2.3. Batch confirmation

If the batch of reference strength employed in the comparative dissolution studies was not the biobatch of the reference strength (batch employed in the *in vivo* bioequivalence study), the following information should be provided:

- Batch number of biobatch
- Justification for use of a batch other than the biobatch
- Comparative dissolution data for batch employed vs. (historical data for) biobatch
- As an Appendix, executed batch manufacturing records (BMR) for batch employed in dissolution studies

<< Please enter information here >>

2.4 Potency (measured content) of reference 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 (CoA) in this biowaiver submission.

<< Please enter information here >>

2.5 COMMENTS FROM REVIEW OF SECTION 2.1 – 2.4 –FOR OFFICIAL USE ONLY

3. Comparison of Test and Reference strengths

3.1. Tabulation of batch information for the test and reference strengths
For solid oral dosage forms the table should contain only the ingredients in tablet core or contents of a capsule. A copy of the table should be filled in for the film coating or hard capsule, if any.

Component and Quality Standard	Function	Strength (label claim)			
		XX mg		XX mg	
		Quantity per unit	%*	Quantity per unit	%*

TOTAL					

**each ingredient expressed as a percentage of the total core*

3.2. Confirmation of Proportionality
Applicant should confirm that the test and reference strength formulations are directly proportional. Any deviations from direct proportionality should be identified and justified in detail.

<< Please enter information here >>

3.3 COMMENTS FROM REVIEW OF SECTION 3.1 – 3.2 –FOR OFFICIAL USE ONLY

4. Comparative *in vitro* dissolution:

Studies comparing different strengths of the test product

- Comparative dissolution data will be reviewed during the assessment of the Quality part of the dossier.
- **As per the Quality guideline (*Guideline on Submission of Documentation for a Multi-source (Generic) Finished Pharmaceutical Product (FPP): Quality Part*, Appendix 1), comparative dissolution studies should be conducted in pH 1.2, 4.5, and 6.8 media. If the proposed dissolution medium for release of the products differs from these media, comparative dissolution data in the proposed release medium should also be provided.**
- Summary information regarding the comparative dissolution studies should be included below to provide a complete summary of the data supporting the biowaiver request.

4.1. Please state the location of:
- the dissolution study protocol(s) in the dossier
- the dissolution study report(s) in the dossier
- the analytical method validation report in the dossier

<< Please enter information here >>

4.2. Summary of the dissolution conditions and method described in the study report(s)
Summary provided below should include the composition, temperature, volume, and method of de-aeration of the dissolution media, the type of apparatus employed, the agitation speed(s) employed, the number of units employed, the method of sample collection including sampling times, sample handling, and sample storage. Deviations from the sampling protocol should also be reported.

4.2.1. Dissolution media: Composition, temperature, volume, and method of de-aeration

<< Please enter information here >>

4.2.2. Type of apparatus and agitation speed(s) employed

<< Please enter information here >>

4.2.3. Number of units employed

<< Please enter information here >>

4.2.4. Sample collection: method of collection, sampling times, method of filtration, sample handling and storage

<< Please enter information here >>

4.2.5. Deviations from sampling protocol

<< Please enter information here >>

4.3. Summarize the results of the dissolution study(s)
Please provide a tabulated summary of individual and mean results with %CV, graphic summary, and any calculations used to determine the similarity of profiles **for each set of experimental conditions**.

<< Please enter information here >>

4.4. Summarize conclusions taken from dissolution study(s)
Please provide a summary statement of the studies performed.

<< Please enter information here >>

4.5. COMMENTS FROM REVIEW OF SECTION 4.1 – 4.4 –FOR OFFICIAL USE ONLY

5. Comparative *in vitro* dissolution:

Studies comparing each strength of the test product to equivalent strength of comparator product; only to be submitted in case *in vitro* dissolution data between different strengths of Test product (see Section 4) are not similar

- This section is applicable in cases where, due to low solubility of the API, similar comparative dissolution between differing strengths is difficult to achieve. The EAC comparator product as identified on the programme's website should be employed.
- Comparative dissolution data will be reviewed during the assessment of the Quality part of the dossier.
- **As per the Quality guideline (*Guideline on Submission of Documentation for a Multi-source (Generic) Finished Pharmaceutical Product (FPP): Quality Part*, Appendix 1), comparative dissolution studies should be conducted in pH 1.2, 4.5, and 6.8 media. If the proposed dissolution medium for release of the products differs from these media, comparative dissolution data in the proposed release medium should also be provided.**
- Summary information regarding the comparative dissolution studies should be included below to provide a complete summary of the data supporting the biowaiver request.

5.1. Purchase, shipment and storage of the comparator product
As per the documentation requirements for comparator products, please attach relevant copies of documents (e.g. receipts) proving the stated conditions.

<< Please enter information here >>

5.2. Potency (measured content) of the comparator product as a percentage of label claim, as measured by the same laboratory under the same conditions as the test product.
This information should be cross-referenced to the location of the Certificate of Analysis (CoA) in this biowaiver submission.

<< *Please enter information here* >>

5.3. Please state the location of:
- the dissolution study protocol(s) in the dossier
- the dissolution study report(s) in the dossier
- the analytical method validation report in the dossier

<< *Please enter information here* >>

5.4. Summary of the dissolution conditions and method described in the study report(s)
Summary provided below should include the composition, temperature, volume, and method of de-aeration of the dissolution media, the type of apparatus employed, the agitation speed(s) employed, the number of units employed, the method of sample collection including sampling times, sample handling, and sample storage. Deviations from the sampling protocol should also be reported.

5.4.1. Dissolution media: Composition, temperature, volume, and method of de-aeration

<< *Please enter information here* >>

5.4.2. Type of apparatus and agitation speed(s) employed

<< *Please enter information here* >>

5.4.3. Number of units employed

<< *Please enter information here* >>

5.4.4. Sample collection: method of collection, sampling times, method of filtration, sample handling and storage

<< *Please enter information here* >>

5.4.5. Deviations from sampling protocol

<< *Please enter information here* >>

5.5. Summarize the results of the dissolution study(s)
Please provide a tabulated summary of individual and mean results with %CV, graphic summary, and any calculations used to determine the similarity of profiles **for each set of experimental conditions**.

<< Please enter information here >>

5.6. Summarize conclusions taken from dissolution study(s)
Please provide a summary statement of the studies performed.

<< Please enter information here >>

5.7. COMMENTS FROM REVIEW OF SECTION 5.1 – 5.6 –FOR OFFICIAL USE ONLY

CONCLUSIONS AND RECOMMENDATIONS –*FOR* OFFICIAL USE ONLY

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.

PART IV:

ZFDA GUIDELINES ON FORMAT AND CONTENT OF SUMMARY OF PRODUCT CHARACTERISTICS FOR PHARMACEUTICAL PRODUCTS

A PRINCIPLES OF PRESENTING INFORMATION

I. The SmPC should be worded in clear and concise language.

II. Each section of the SmPC should first deal with those issues that apply to the core population for whom the medicine is indicated followed (when necessary) by specific information for any relevant special population (e.g. children or elderly).

III. Consistent medical terminology from the Medical Dictionary for Regulatory Activities (MedDRA) should be used throughout the SmPC.

IV. The SmPC provides information on a particular medicinal product; therefore, it should not include reference to other medicinal products (e.g. through statement such as "Like other medicines of the same class …") except when it is a class warning recommended by a competent authority.

B SMPC FORMAT AND CONTENT

The SmPC will be structured and populated as outlined in 1-10 below.

1. NAME OF THE MEDICINAL PRODUCT

Both the strength and the pharmaceutical form should follow the proprietary name. However, when otherwise referring to the medicinal product throughout the SmPC text, the strength and the pharmaceutical form do not have to be mentioned in the name. The International Non-proprietary Name (INN) or the usual common name of the active substance should be used when referring to properties of the active substance(s) rather than those of the product. The use of pronouns (e.g. "it") is encouraged whenever possible.

Strength

The strength should be the relevant quantity for identification and use of the product and should be consistent with the quantity stated in the quantitative composition and in the posology. Different strengths of the same medicinal product should be stated in the same way, e.g. 250 mg, 500 mg, 750mg. The use of decimal points should be avoided where these can be easily removed (e.g. 250 microgram, not 0.25 mg). However, where a range of medicinal products of the same pharmaceutical form includes strengths of more than one unit (e.g. 250 microgram, 1 mg and 6 mg), it may be more appropriate in certain cases to state the strengths in the same unit for the purpose of comparability (e.g. 0.25 mg, 1 mg and 6 mg). For safety reasons, micrograms and millions (e.g. for units) should always be spelled out in full rather than be abbreviated.

Pharmaceutical form

The pharmaceutical form of a medicinal product should be described by ZFDA standard term (see Appendix 1). No reference should be made to the route of administration or container unless these elements are part of the standard term or where there is a particular safety reason for their inclusion or where there are identical products, which may be distinguished only by reference to the route of administration or to the container.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Full details of the qualitative and quantitative composition in terms of the active substance(s) andexcipients, knowledge of which are essential for proper administration of the medicinal product,should be provided in section 2 of the SmPC and as appropriate in section 4.3 or 4.4. Excipients which are required to be declared on the labelling (see ZFDA *Guidelines on Format and Content of Labels for Medicinal Product*s) should be stated here under a separate subheading qualitatively, and, quantitatively.The following standard statement should be included at the end of the section, i.e. 'for full list ofexcipients, see section 6.1'.

If a diluent is part of the medicinal product, information should be included in the relevant sections(usually sections 3, 6.1, 6.5 and 6.6).

Qualitative declaration

The active substance should be declared by its recommended INN accompanied by its salt or hydrateform if applicable. References to the
pharmacopoeial quality should not be included.

Quantitative declaration

The quantity of the active substance should be expressed per dosage unit (for metered dose inhalationproducts, per delivered dose and/or per metered dose), per unit volume, or per unit of weight andshould be related to the declaration of strength in section 1.

Quantity should be expressed in internationally recognised standard term which could becomplemented with another term if more meaningful to healthcare professionals.

Salts and hydrates

Where the active substance is present in the form of a salt or hydrate, the quantitative compositionshould be expressed in terms of the mass (or biological activity in International (or other) units whereappropriate) of the active moiety (base, acid or anhydrous material), e.g. '60 mg toremifene (as
citrate)' or toremifene citrate equivalent to 60 mg toremifene'.

Where a salt is formed *in situ* during the preparation of the finished product (i.e. formed during themixture of a solvent and powder), the quantity of the active moiety should be stated, with a referenceto the *in situ* formation of the salt.

In the case of established active substances in medicinal products where the strength has traditionallybeen expressed in the form of a salt or hydrate, the quantitative composition may be declared in termsof the salt or hydrate, e.g. '60 mg diltiazem hydrochloride'. This may also apply when the salt is formed *in situ.*

Esters and pro-drugs

If the active substance is an ester or pro-drug, the quantitative composition should be stated in terms ofthe quantity of the ester or pro-drug. When the active moiety is an active substance of an alreadyapproved medicinal product, the quantitative composition should also be stated in terms of the quantity of this active moiety (e.g. 75 mg of fosphenytoin is equivalent to 50 mg of phenytoin).

Oral powders for solution or suspension

The quantity of active substance should be stated per unit dose if the product is a single-dosepreparation or otherwise per unit dose volume after reconstitution; a reference to the molarconcentration may also be appropriate in some cases.

Parenterals excluding powders for reconstitution

For single-dose parenterals, where the total contents of the container are given in a single dose ('totaluse'), the quantity of active substance(s) should be stated per presentation (e.g. 20 mg etc.) notincluding any overages or overfill. The quantity per ml and the total labelled volume should also be given.

For single-dose parenterals, where the amount to be given is calculated on the basis of the patient'sweight or body surface or other variable ('partial use'), the quantity of active substance(s) should bestated per ml. The quantity per total labelled volume should also be given. Overages or overfills should not be included.

For multi-dose and large volume parenterals, the quantity of active substance(s) should be stated perml, per 100 ml, per 1000 ml, etc. as appropriate, except for multidose vaccines containing 'n' doses ofthe same dose. In this case, the strength should be expressed per dose volume. Overages or overfillsshould not be included.

Where appropriate, e.g. for X-ray contrast media, and parenterals containing inorganic salts, thequantity of active substance(s) should also be indicated in millimoles. For X-ray contrast media withiodine-containing actives substances, the quantity of iodine per ml should be stated in addition to the quantity of the active substance.

Powders for reconstitution prior to parenteral administration

When the product is a powder to be reconstituted prior to administration, the total quantity of activesubstance in the container should be stated not including

overages or overfills, as well as the quantityper ml when reconstituted, unless there are several means of reconstituting, or different quantitiesused, which result in different final concentrations.

Concentrates

The quantity should be stated as the content per ml in the concentrate and as the total content of theactive substance. The content per ml when diluted as recommended should also be included unless theconcentrate is to be diluted to within a range of different final concentrations.

Transdermal patches

The following quantitative details should be given: the content of active substance(s) per patch, themean dose delivered per unit time, and the area of the releasing surface, e.g. 'Each patch contains 750micrograms of estradiol in a patch size of 10 cm2, releasing a nominal 25 micrograms of estradiol per24 hours'.

Multidose solid or semi-solid products

Quantity of active substance should be stated, where possible, per unit dose, otherwise per gram, per 100 g or percentage, as appropriate.

Biological medicinal products

Expression of strength

The quantity of biological medicinal products should be expressed in terms of mass units, units of biological activity, or International Units as appropriate for the particular product.

The biological origin of the active substance

The origin of the active substance should be defined briefly. Thus, the nature of any cellular system(s) used for production and, if relevant, the use of recombinant DNA technology should be specified. The entry should take the form: "produced in XXX cells <by recombinant DNA technology>". The following are examples of the application of this principle:

"produced in human diploid (MRC-5) cells",

"produced in *Escherichia coli* cells by recombinant DNA technology",

"produced in chick-embryo cells",

"produced from the plasma of human donors",
"produced from human urine",

"produced from <animal>blood",

"produced from porcine pancreatic tissue",

"produced from porcine intestinal mucosa".

Special provisions for normal immunoglobulins

In the case of normal immunoglobulins, the IgG subclass distribution should be stated in terms of percent of total IgG present. The upper limit of the IgA content should follow.

Special provisions for vaccines

In the case of vaccines, the content of active substance per dose unit (e.g. per 0.5 ml) should be stated.
Adjuvants, if present, should be stated qualitatively and quantitatively.

Residues that are of special relevance (e.g. ovalbumin in egg derived vaccines) should be specified.

Additional specific guidance is available in CHMP guidelines on biotechnological medicinal products, e.g. the CHMP Guideline on the Pharmaceutical Aspects of the Product Information for Human Vaccines.

Herbal medicinal products

The quantitative declaration should be in accordance with the existing quality guidelines on herbal medicinal products.

3. PHARMACEUTICAL FORM

The pharmaceutical form should be described by a full standard term of the ZFDA using the singular form. The term used in this section should be the same as the term used in section 1. A visual description of the appearance of the product (colour, markings, etc.) should be given, in a separate paragraph to the standard term, including information on the actual size of a solid oral formulation, e.g. In case of tablets designed with a score line, information should be given on whether or not reproducible dividing of the tablets has been shown. e.g. 'the score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses', 'the tablet can be divided into equal halves'.

Information on pH and osmolality should be provided, as appropriate. In case of products to be reconstituted before use, the appearance before reconstitution should be stated in this section. Appearance of the product after reconstitution should be stated in sections 4.2and 6.6.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The indication(s) should be stated clearly and concisely and should define the target disease or condition distinguishing between treatment (symptomatic, curative or modifying the evolution or progression of the disease), prevention (primary or secondary) and diagnostic indication. When appropriate it should define the target population especially when restrictions to the patient populations apply.

Study endpoints should not normally be included. The objective of a prevention indication may be mentioned in general terms only. This should also be done for the target population.

Where results from subsequent studies provide further definition or information on an authorized indication, such information, provided it does not itself constitute a new indication, may be considered for inclusion in section 5.1.

Mandatory conditions of product usage not covered more appropriately in other parts of the SmPC may also be included when relevant, e.g. concomitant dietary measures, lifestyle changes, or other therapy.

It should be stated in which age groups the product is indicated, specifying the age limits, e.g. 'X is indicated in <adults><neonates><infants><children><adolescents><aged x to y<years, months>>.

If the product's indication depends on a particular genotype or the expression of a gene or a particular phenotype, this should be stated in the indication.

4.2 Posology and method of administration

In case of restricted medical prescription, this section should be started by specifying the conditions.

In case of specific safety need, any recommended restriction to a particular setting should also be stated (e.g. "*restricted to hospital use only*" or "*appropriate resuscitation equipment should be availa*ble").

Posology

The dosage should be clearly specified for each method/route of administration and for each indication, as appropriate.

Where appropriate, a reference to official recommendations should be made (e.g. for primary vaccination and antibiotics as well as for booster dose).
Dose recommendations (e.g. mg, mg/kg, mg/m^2) should be specified per dose interval for each category where appropriate (specify age/weight/body surface area of subsets of the population as appropriate). Frequency of dosing should be expressed using time units (e.g. once or twice daily or every 6 hour) and, to avoid confusion, abbreviations e.g. OD or BID should not be used.

Where appropriate, the following points should be addressed:

- the maximum recommended single, daily and/or total dose,
- the need for dose titration,
- the normal duration of use and any restrictions on duration and, if relevant, the need for tapering off, or advice on discontinuation,
- advice on action to be taken if one or more dose(s) is (are) missed, or e.g. in case of vomiting(the advice should be as specific as possible, taking into

consideration the recommended frequency of dosing and relevant pharmacokinetic data)

- advice on preventive measures to avoid certain adverse drug reactions (e.g. administration of antiemetic's) with cross-reference to section 4.4,

- the intake of the product in relation to drink and food intake, together with a cross-reference to section 4.5 in case of specific interaction e.g. with alcohol, grapefruit or milk,

- advice regarding repeat use, with any information on intervals to be observed between courses of treatment, as appropriate,

- Interactions requiring specific dose adjustments with cross-reference to other appropriate sections of the SmPC (e.g. 4.4, 4.5, 4.8, 5.1, 5.2), and

- it may also be relevant to recommend not to prematurely discontinue a treatment in case of specific non-serious adverse reaction(s) that are frequent but transient or manageable with dose titration.

Where relevant to the particular product, the following should appear 'The potency of this medicinal product is expressed in <proprietary name> units. These units are not interchangeable with the units used to express the potency of other <active substance name> preparations'.

Special populations

Dosage adjustments or other posology related information in specific patient groups should be stated where necessary, in well-defined sub-sections ordered by importance, e.g. regarding:

- elderly population; it should be made clear whether or not any dosage adjustment is necessary in any subsets of the elderly population, with cross-reference to other sections providing information in elderly, e.g. 4.4, 4.5, 4.8 or 5.2.

- renal impairment; the dose recommendation should relate as precisely as possible to the cut-off values for biochemical markers of renal impairment in clinical studies and to the results of these studies;

- hepatic impairment, specified according to the patients included in studies, for instance 'alcohol-related cirrhosis' and the definitions used in the studies, for instance Child-Pugh score/grade of the patients;

- patients with a particular genotype; with cross-reference to other relevant sections for further detail as appropriate;

- other relevant special population (e.g. patients with other concomitant disease or overweight patients).

Advice relevant for dosage adjustment e.g. from monitoring of clinical symptoms and signs, and/or laboratory investigations, including blood concentrations of the

medicinal product should be mentioned when appropriate with cross-reference to other sections where appropriate.

Paediatric population

The specific sub-section 'paediatric population' should always be included and the information given should cover all subsets of the paediatric population, using a combination of the possible situations presented below as appropriate.

If the product is indicated in the paediatric population, posology recommendations should be given for each of the relevant subsets. The age limits should reflect the benefit-risk assessment of the available documentation for each subset.

If the posology is the same in adults and children, then a statement to this effect is sufficient; the posology does not need to be repeated.

Dose recommendations (e.g. mg, mg/kg, mg/m^2) should be specified per dose interval for the paediatric subsets where the product is indicated. Different subsets may require different dosing information. If necessary, recommendations in preterm and new borns should be presented taking into account the more appropriate age e.g. gestational age or the post-menstrual age.

Depending on the subset, the clinical data and available formulations, the dose will be expressed according to weight or body surface area, e.g. "*children aged 2-4 years, 1 mg/kg bodyweight twice a day*".

When appropriate, information on timing of intake of the product should consider children's daily life, e.g. school or sleep.

Where a product is indicated in children and no adequate paediatric formulation can be developed, detailed instructions on how to obtain an extemporaneous preparation shall be included in section 6.6 with a cross-reference in section 4.2.

Doses and method of administration in the various subsets may be presented in a tabulated format.

If there is no indication for the product in some or all subsets of the paediatric population, no posology recommendation can be made, but available information should be summarized using the following standard statements (one or combination of several as appropriate):

- The <safety><and><efficacy> of X in children aged x to y<months, years><*or any other relevant subsets e.g. weight, pubertal age, gender*><has><have> not <yet> been established.

One of the following statements should be added:

– <No data are available>.

or

– <Currently available data are described in section <4.8><5.1><5.2>but no recommendation on a posology can be made >

- X should not be used in children aged x to y<years, months><*or any other relevant subsets e.g. weight, pubertal age, gender*> because of

<safety><efficacy> concern(s) <*concern(s) to be stated* with cross-reference to sections detailing data (e.g. 4.8 or 5.1) >.

- There is no relevant use of X in <the paediatric population><in children aged x to y><years, months>><*or any other relevant subsets e.g. weight, pubertal age, gender*> in the indication(s)
  <specify indication(s)>.

- X is contraindicated in children aged x to y<years, months><*or any other relevant subsets e.g. weight, pubertal age, gender*><in the indication …> (cross-reference to section 4.3).

If there are more appropriate strength(s) and/or pharmaceutical form(s) for administration in some or all subsets of the paediatric population (e.g. oral solution for infants), these can be mentioned in section 4.2 of the SmPC of the less appropriate one(s).

E.g.: Other pharmaceutical forms/strengths may be more appropriate for administration to this population.

Method of administration

Any special precautions related to the manipulation or administration of the product (e.g. cytotoxic products) by healthcare professionals (including pregnant healthcare professionals), the patient or carers should be mentioned here under a specific sub-heading (<*Precaution to be taken before manipulating or administering the product*>), with a cross-reference to section 6.6 (or 12).

The route of administration and concise relevant instruction for correct administration and use should be given here. Information on instructions for preparation or reconstitution should be placed in section6.6 'Special precautions for disposal of a used medicinal product and other handling of the product' (or in section 12 if appropriate) and cross-referenced here.
When supportive data are available, information on alternative method(s) to facilitate administration or acceptability should be given as explicitly as possible (e.g. possibility of crushing tablet, cutting tablet or transdermal patch, pulverizing tablet, opening capsules, mixing with food, dissolution in drinks – specifying if a proportion of the dose can be given) particularly for administration via feeding tubes.

Any specific recommendation for use related to the pharmaceutical form should be explained, e.g.:
- "the coated tablet should not be chewed because of <bad taste>,
- "the enteric-coated tablet should not be crushed because coating prevents <pH sensitive degradation><irritant effects> on the gut",
- "the coated tablet should not be broken because the coating is intended to ensure a prolonged release (see 5.2)".

For parenteral formulations, information on the rate or speed of injection or infusion should be provided.

For parenteral formulations - in children, especially newborns in whom quite often fluids have to be restricted - it would be useful to have information on maximal

concentration that can be safely administered (e.g. "*no more than X mg of Y/ml of solution*").

4.3 Contraindications

Situations where the medicinal product must not be given for safety reasons, i.e. contraindications, are the subject of this section. Such circumstances could include a particular clinical diagnosis, concomitant diseases, demographic factors (e.g. gender, age) or predispositions (e.g. metabolic or immunological factors, a particular genotype and prior adverse reactions to the medicine or class of medicines). The situations should be unambiguously, comprehensively and clearly outlined.

Other medicines or classes of medicine, which must not be used concomitantly or consecutively should be stated, based on either data or strong theoretical reasons. If applicable a cross-reference to section 4.5 should be made.

In general, patient populations not studied in the clinical trial programme should be mentioned in section 4.4 and not in this section unless a safety issue can be predicted (e.g. use of renally eliminated substances with narrow therapeutic margin in renal failure patients). If, however, patients have been excluded from studies due to a contraindication on grounds of safety, they should be mentioned in this section. If applicable a cross-reference to section 4.4 should be made.

Only if pregnancy or breastfeeding is contraindicated, should it be mentioned here. In section 4.6, a cross-reference should be made and further background information provided.
Hypersensitivity to the active substance or to any of the excipients or residues from the manufacturing process should be included, as well as any contraindication arising from the presence of certain excipients.

For herbal medicinal products, hypersensitivity extended to other plants of the same family or to other parts of the same plant should be labelled as a contraindication, where applicable.

Lack of data alone should not lead to a contraindication. Where for safety reasons, the product should be contraindicated in a specific population, e.g. paediatric or a subset of the paediatric population, it should appear in this section with a cross-reference to the section giving detailed information on the safety issue. A contraindication in the paediatric population should be listed without a sub-heading.

4.4 Special warnings and precautions for use

The order of warnings and precautions should in principle be determined by the importance of the safety information provided.

The exact content of this section will be different for each product and the therapeutic conditions it is intended to treat. It is however suggested that the following items should be included where relevant to the specific product.

Information on a specific risk should be given in section 4.4 only when the risk leads to a precaution for use or when healthcare professionals have to be warned of this risk. Patient groups in which use of the medicinal product is contraindicated should be mentioned in section 4.3 only and not to be repeated here.

The following should be described:

- The conditions, in which the use of the medicinal product could be acceptable, provided that special conditions for use are fulfilled. In particular, specific risk minimization measures requested as part of a Risk Management Plan to ensure safe and effective use should be described in this section. (*For example; "Liver function should be monitored before initiation of treatment and monthly thereafter", "Patients should be advised to immediately report any symptoms of depression and/or suicidal ideation",* "*Women of childbearing potential should use contraception", …)*

- Special patient groups that are at increased risk or are the only groups at risk of experiencing product or product class-related adverse reactions (usually serious or common), e.g. elderly, children, patients with renal or hepatic impairment (including the degree of impairment, e.g. mild, moderate or severe), patients having an anaesthetic or patients with cardiac failure. Cross-reference to section 4.8 on the differential effects in terms of frequency and severity of the specified adverse reaction should be provided.

- Serious adverse reactions to which healthcare professionals need to be alerted, the situations in which these may occur and the action that may be required, e.g. emergency resuscitation.

- If there are particular risks associated with starting the medicinal product (e.g. first dose effects) or stopping it (e.g. rebound, withdrawal effects), these should be mentioned in this section, together with the action required for prevention.

- Any measures which can be taken to identify patients at risk and prevent the occurrence, or detect early the onset or worsening of noxious conditions. If there is a need for awareness of symptoms or signs representing early warning of a serious adverse reaction, a statement should be included.
- Any need for specific clinical or laboratory monitoring should be stated. Recommendation for monitoring should address why, when and how the monitoring should be conducted in clinical practice. If dose reduction or other posology is recommended in such circumstances or conditions, this should be included in section 4.2 and cross-referenced here.

- Any warnings necessary for excipients or residues from the manufacturing process.

- For herbal preparations containing alcohol, information about the ethanol content in the medicinal product should be included in accordance with the Guideline on excipients in the label and package leaflet of medicinal products for human use.
- Any warnings necessary with respect to transmissible agents.

- Subjects or patients with a specific genotype or phenotype might either not respond to the treatment or be at risk of a pronounced pharmacodynamics effect or adverse reaction. These may arise because of non-functioning enzyme alleles, alternative metabolic pathways (governed by specific alleles), or transporter deficiencies. Such situations should be clearly described if known.

- Any particular risk associated with an incorrect route of administration (e.g. necrosis risk with extravasation of intravenous formulation, or neurological consequences of intravenous use instead of intramuscular use), should be presented, with advice on management if possible.

In exceptional cases, especially important safety information may be included in bold type within a box.

Any adverse reactions described in this section or known to result from conditions mentioned here should also be included in section 4.8.

Specific interference with laboratory tests should be mentioned when appropriate, e.g. Coombs test and Beta-lactams. They should be clearly identified with a subheading, e.g. "*Interference with serological testing*".

In general, descriptions of warnings and precautions regarding pregnancy and breast-feeding, ability to drive and use machines, and other aspects of interactions should be dealt with in sections 4.6, 4.7 and4.5, respectively. However in specific cases of major clinical importance it might be more appropriate to describe specific precautionary measures in this section, e.g. contraception measures, or when concomitant use of another medicine is not recommended, and with cross reference to section 4.5, 4.6, or 4.7.

Paediatric population

When the product is indicated in one or more subsets of the paediatric population and there are warnings and precautions for use that are specific to the paediatric population or any subset of the paediatric population, they should be identified under this subheading. Any necessary warning or precaution in relation to long-term safety (e.g. on growth, neuro-behavioural development or sexual maturation) or specific monitoring (e.g. growth) in the paediatric population should be described.

When long-term safety data are necessary but not yet available, it should be stated in this section. Warnings should be included in case of possible significant or long-lasting impact on children's daily activities, such as learning ability or physical activities, or in case of impact on appetite or sleep pattern.

If measures are requested that are specific to the paediatric population for which the product is indicated (e.g. as part of a Risk Management Plan), these measures should be described in this section.

4.5 Interaction with other medicinal products and other forms of interaction

This section should provide information on the potential for clinically relevant interactions based on the pharmacodynamics properties and *in vivo* pharmacokinetic studies of the medicinal product, with a particular emphasis on the interactions, which result in a recommendation regarding the use of this medicinal product. This includes *in vivo* interaction results, which are important for extrapolating an effect on a marker ('probe') substance to other medicinal products having the same pharmacokinetic property as the marker.

Interactions affecting the use of this medicinal product should be given first, followed by those interactions resulting in clinically relevant changes on the use of others.
Interactions referred to in other sections of the SmPC should be described here and cross-referenced from other sections.

The order of presentation should be contraindicated combinations, those where concomitant use is not recommended, followed by others.

The following information should be given for each clinically relevant interaction:

a) Recommendations: these might be

- Contraindications of concomitant use (cross-refer to section 4.3),
- Concomitant use not recommended (cross-refer to section 4.4), and
- Precautions including dose adjustment (cross-refer to sections 4.2 or 4.4, as appropriate), mentioning specific situations where these may be required.

b) Any clinical manifestations and effects on plasma levels and AUC of parent compounds or active metabolites and/or on laboratory parameters.

c) Mechanism, if known. For example, interaction due to inhibition or induction of cytochrome P450 should be presented as such in this section, with a cross-reference to 5.2 where *in vitro* results on inhibition or induction potential should be summarized.

Interactions not studied *in vivo* but predicted from *in vitro* studies or deducible from other situations or studies should be described if they result in a change in the use of the medicinal product, cross-referring to sections 4.2 or 4.4.

This section should mention the duration of interaction when a medicinal product with clinically important interaction (e.g., enzyme inhibitor or inducer) is discontinued. Adjustment of dosing may be required as a result. The implication for the need for a washout period when using medicines consecutively should also be mentioned.

Information on other relevant interactions such as with herbal medicinal products, food, alcohol, smoking, or pharmacologically active substances not used for medical purpose, should also be given. With regard to pharmacodynamics effects where there is a possibility of a clinically relevant potentiation or a harmful additive effect, this should be stated.

In vivo results demonstrating an absence of interaction should only be mentioned here if this is of major importance to the prescriber (e.g. in therapeutic area where potentially problematic interactions have been identified such as with anti-retroviral medicines).

If no interaction studies have been performed, this should be clearly stated.

Additional information on special populations

If there are patient groups in which the impact of an interaction is more severe, or the magnitude of an interaction is expected to be larger e.g., patients with decreased renal function (in case the parallel pathway is renal excretion), paediatric patients, elderly e.t.c, this information should be given here.

If interactions with other medicinal products depend on polymorphisms of metabolizing enzymes or certain genotypes, this should be stated.

Paediatric population

Information specific to a subset of the paediatric population should be given here if there is an indication for the particular age group.
The resulting exposure and clinical consequences of a pharmacokinetic interaction can differ between adults and children, or between older and younger children. Therefore;

- any identified treatment recommendations should be given in relation to concomitant use in the paediatric subset(s) (e.g. dose adjustment, extra-monitoring of clinical effect marker/adverse reactions, therapeutic drug monitoring),

- If the interaction studies have been performed in adults, the statement 'Interaction studies have only been performed in adults' should be included.

- If the extent of an interaction is known to be similar in a paediatric age group to that in adults, this should be stated.

- If this is not known, this should also be stated.

The same applies to pharmacodynamics drug interactions.

In cases of food interaction leading to a recommendation on co-administration with a meal or specific food, it should be specified whether this is relevant for paediatric use (especially newborns and infants) whose diet is different (100 % milk in newborns).

Overall, section 4.5 should be presented in the simplest possible way to highlight the interactions resulting in a practical recommendation regarding the use of the medicinal product. Presentation in a tabulated format may help where interactions are numerous and various, such as with anti-viral products.

4.6 Fertility, pregnancy and lactation

General principles

Efforts should be made by the Marketing Authorization Applicant or Holder to provide the reasons for the recommendations for use in pregnant or lactating women and in women of childbearing potential.
This information is important for the healthcare professionals informing the patient.

In the overall assessment, all available knowledge should be taken into account, including clinical studies and post-marketing surveillance, pharmacological activity, results from non-clinical studies, and knowledge about compounds within the same class.

Efforts should be made to update the recommendations for use during pregnancy and lactation on the basis of increasing human experience in exposed pregnancies, which eventually supersede the animal data.

In case of contraindication, this should be included in section 4.3.

The following should be mentioned:

Women of childbearing potential / Contraception in males and females

Recommendations on the use of the medicinal product in women of childbearing potential should be given when appropriate including the need for pregnancy test or contraceptive measures. Where an effective contraception is required for patients or partners of patients during treatment or for a defined period before starting or after ending treatment, the rationale should be included in this section. If contraceptive measures are recommended, there should also be a cross-reference to section 4.5 (and possibly 4.4) in case of interaction with oral contraceptives.

Pregnancy

In general, clinical and non-clinical data should be followed by recommendations.

With respect to non-clinical data,

- only conclusions of the reproductive toxicity studies should be included in this section. Further details should be provided in section 5.3.

With respect to clinical data,

- the section should include comprehensive information on relevant adverse events reported in the embryo, the foetus, neonates and pregnant women, when appropriate. The frequency of such events (for example the frequency of birth defects) should be specified when available.
- the section should specify the extent of the human experience if no adverse events have been reported in pregnancy.

With respect to the recommendations:

- Recommendations on the use of the medicinal product during the different periods of gestation, including the reason(s) for these recommendations, should be given.

- Recommendations for the management of exposure during pregnancy when appropriate (including relevant specific monitoring such as foetal ultrasound, specific biological or clinical surveillance of the foetus or the neonate) should be given.

Cross-references can be included in sections 4.3, 4.4 and 4.8, as appropriate.

Breastfeeding

If available, clinical data should be mentioned (exposed breastfed infants) as the conclusions of kinetic studies (plasma concentrations in breastfed infants, transfer of the active substance and/or its metabolite(s) into human milk…). Information on adverse reactions in nursing neonates should be included if available.

Conclusions from non-clinical studies on the transfer of the active substance and/or its metabolite(s) into milk should be given only if no human data are available.

Recommendations should be given to stop or continue breastfeeding and/or to stop or continue the treatment in cases where treatment or breastfeeding discontinuation is recommended, and the reason should be provided.

Fertility

The main information on the possible effects of the medicinal product on male and female fertility should be included in section 4.6.

This section should include:

a) Clinical data if available.

b) Relevant conclusions from nonclinical toxicity studies, if available. Further details should be included in section 5.3.

c) Recommendations for the use of the medicinal product when pregnancy is planned but fertility might be affected by treatment.

Cross-references could be included in section 4.3, if appropriate.

If there are no fertility data at all, then this should be clearly stated.

4.7 Effects on ability to drive and use machines

On the basis of the pharmacodynamics and pharmacokinetics profile, reported adverse reactions and/or specific studies in a relevant target population addressing the performance related to driving and road safety or using machines, specify whether the medicinal product has a) no or negligible influence b) minor influence, c) moderate influence or d) major influence on these abilities. Other important factors that affect the ability to drive and use machines should be considered if

known, e.g. duration of the impairing effect and the development of tolerance or adverse reactions with continued use.

For situations c and d, special warnings/precautions for use should be mentioned here (and also in section 4.4 for situation d).

4.8 Undesirable effects

This section should include all adverse reactions from clinical trials, post-authorization safety studies and spontaneous reporting for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or on findings from epidemiological studies and/or on an evaluation of causality from individual case reports. Adverse events, without at least a suspected causal relationship, should not be listed in the SmPC.

The content of this section should be justified in the Clinical Overview of the marketing authorization application based upon a best-evidence assessment of all observed adverse events and all facts relevant to the assessment of causality, severity and frequency. This section should be regularly reviewed and, if necessary, updated with the aim to ensure appropriate information to health care professionals on the safety profile of the product.

It is important that the whole section is worded in concise and specific language and does not include information such as claims regarding the absence of specific adverse reactions, comparative frequency statements other than as described below, or statements of general good tolerability such as “well tolerated”, “adverse reactions are normally rare”, etc. Statements on lack of proof of causal association should not be included.

In order to provide clear and readily accessible information, section 4.8 should be structured according to the following recommendations:
a. Summary of the safety profile
b. Tabulated summary of adverse reactions
c. Description of selected adverse reactions
d. <Paediatric population>
e. <Other special population(s)>

a. Summary of the safety profile

The summary of the safety profile should provide information about the most serious and/or most frequently occurring adverse reactions.

If known, it may be helpful to indicate the timing when adverse reactions occur. For example, in order to prevent early discontinuation of a treatment, it may be important to inform about non-serious adverse reactions that are frequent in the beginning of the treatment but may disappear with its continuation. Another example would be to inform about adverse reaction associated with long-term use. Frequencies of cited adverse reactions should be stated as accurately as possible. This summary of the safety profile should be consistent with the important identified risks mentioned in the Safety Specification of the Risk Management Plan.

The information should be consistent with the Table of Adverse Reactions (see section b). Cross-reference should be made to section 4.4 if relevant risk minimization measures have been proposed in that section.

An example of an acceptable statement is given below:

'At the beginning of the treatment, epigastric pain, nausea, diarrhoea, headache or vertigo may occur; these reactions usually disappear within a few days even if treatment is continued. The most commonly reported adverse reactions during treatment are dizziness and headache, both occurring in approximately 6% of patients. Serious acute liver injury and agranulocytosis may occur rarely (less than 1 case per 1,000 patients)'

b. Tabulated list of adverse reactions

A single table (or structured listing) should list all adverse reactions with their respective frequency category. In some cases for common or very common reactions, and when it is necessary for the clarity of the information, frequency figures may be presented in the table.

Separate tables are acceptable in exceptional cases where the adverse reaction profiles markedly differ depending on the use of the product. For example, it might be the case for a product used for different indications (e.g. an oncology and a non-oncology indication) or at different posologies.

The table should be introduced with a short paragraph stating the source of the safety database (e.g. from clinical trials, post-authorization safety studies or spontaneous reporting).

The table should be presented according to the MedDRA system organ classification. The system organ class (SOC) should be presented in the order shown in the annex. Adverse reactions descriptions should be based on the most suitable representation within the MedDRA terminology. This will usually be at the Preferred Term (PT) Level, although there may be instances where the use of Lowest Term Level or exceptionally group terms, such as High Level Terms may be appropriate. As a general rule, any adverse reactions should be assigned to the most relevant SOC related to the target organ. For example, PT '*Liver function test abnormal*' should be assigned to the SOC '*Hepatobiliary disorders*' rather than to the SOC '*Investigations*'.

Within each system organ class, the adverse reactions should be ranked under headings of frequency, most frequent reactions first. Within each frequency grouping, adverse reactions should be presented in the order of decreasing seriousness. The names used to describe each of the frequency groupings should follow standard terms established in each official language using the following convention: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

In exceptional cases, if a frequency cannot be estimated from the available data, an additional category frequency 'not known' may be used. In case the expression *"Frequency not known"* is used, the following text should be added in the list of terms explaining the frequency categories: *"not known (cannot be estimated from the available data)"*. The expressions isolated/single cases/reports should not be used.

Where additional details about an adverse reaction are described in section c), the reaction concerned should be highlighted, for example with an asterisk, and, “see section c)” should be included as a footnote.

Guidance on how to estimate the frequency of an adverse reaction is provided at the end of this chapter of the guideline.

d) Description of selected adverse reactions

This section should include information characterizing specific adverse reaction which may be useful to prevent, assess or manage the occurrence of an adverse reaction in clinical practice.

This section should include information characterizing individual serious and/or frequently occurring adverse reactions, or those where there have been reports of particularly severe cases. The information should provide frequency and may describe for example reversibility, time of onset, severity, duration, mechanism of the reaction (if of clinical relevance), dose relationship, relationship with duration of exposure or risk factors. Measures to be taken to avoid specific adverse reactions or actions to be taken if specific reactions occur should be mentioned under section 4.4 and cross-referenced here.

Information on the occurrence of withdrawal reactions may be mentioned here with cross-reference to section 4.2 in case of need for tapering off or advice on discontinuation of the product.

Mention should be made here of any differences between different dosage forms in respect of adverse reactions.

In the case of combination products, information should be included in this sub-section pointing out which particular adverse reactions are usually attributable to which active substance of the combination, where known.

Any adverse reactions resulting directly from an interaction should be mentioned here and cross-referenced to section 4.5.

This section should also inform on adverse reactions with very low frequency or with delayed onset of symptoms which may not have been observed in relation to the product, but which are considered to be related to the same therapeutic, chemical or pharmacological class. The fact that this is a class attribution should be mentioned.

Any adverse reaction specific to excipients or residues from the manufacturing process should be included.

e) <Paediatric population>

A paediatric sub-section should always be included (unless irrelevant).

The extent and age characteristics of the safety database in children should be described (e.g. from clinical trials or pharmacovigilance data). Uncertainties due to limited experience should be stated.

If the observed safety profile is similar in children and adults this could be stated: e.g. “Frequency, type and severity of adverse reactions in children are <expected> to be the same as in adults”. Similarly, it is appropriate to state whether the safety profiles in the different paediatric subsets are similar or not.

Any clinically relevant differences (i.e. in nature, frequency, seriousness or reversibility of adverse reactions) between the safety profiles in adult and paediatric populations, or in any relevant age groups, should be described and presented by age group. If there is a need for specific monitoring, this should be highlighted by cross-referencing to section 4.4. For clinically relevant differences, a separate table listing such adverse reactions by frequency can be added and presented by relevant age groups if appropriate. If some paediatric adverse reactions are considered common (≥1/100 to <1/10) or very common (≥1/10), the frequencies should be provided in parentheses.

In case of major difference with the safety profile in adults, a summary of the safety profile in children could be presented to facilitate the presentation of the information. Available information, from any source scientifically validated, on long-term safety in children (e.g. on growth, mental development and sexual maturation) should also be summarized, whether positive or negative, with cross-reference to section 5.1 if appropriate. Any risk factors such as duration of treatment or period at risk should be specified.

If relevant, symptoms of neonatal withdrawal should be listed in a separate paragraph with cross-reference with 4.6

e. <Other special populations>

This section may include information on any clinically relevant differences (i.e. in nature, frequency, seriousness or reversibility of adverse reactions, or need for monitoring) specifically observed in other special populations such as elderly, patients with renal impairment, patients with hepatic impairment, patients with other diseases or a specific genotype. Cross-reference to other sections such as 4.3, 4.4 or 4.5 may be added as appropriate.

Adverse reactions may also be related to genetically determined product metabolism. Subjects or patients deficient in the specific enzyme may experience a different rate or severity of adverse reactions. This should be mentioned and where relevant correlated with data from clinical trials.

Further guidance on the estimation of frequency of adverse reactions

The estimation of the frequency of an adverse reaction depends on the data source (i.e. clinical trial, post-authorization safety study or spontaneous reporting), the quality of data collection and causality evaluation. If the choice of the frequency category is based on different sources, the category representing the highest frequency should be chosen unless a more specific method has been applied and thus resulted in an estimate of clearly higher validity, e.g. a pooled analysis across suitable studies.

Sources of data should use population exposed to the doses and treatment duration as recommended in the SmPC.

Reactions that are reported under different terms but represent the same phenomenon (e.g., sedation, somnolence, drowsiness) should ordinarily be grouped together as a single adverse reaction to avoid diluting or obscuring the true effect. Similarly, reactions that represent a syndrome complex should ordinarily be grouped together under an appropriate heading to avoid obscuring the full range of respective symptoms.

Adverse reactions from clinical trials

Safety data from several studies should be pooled to increase the precision of adverse reaction rates as appropriate without introducing bias (e.g. major difference in population characteristics or exposure to the product).

The frequency of adverse reactions should be derived from pooled placebo-controlled studies if these data are available and the databases are sufficiently large to be informative. If these data are unavailable or not sufficiently informative, active-controlled data or possibly single-arm or add-on trials databases could be used to estimate frequencies.

Frequency should represent crude incidence rates (and not differences or relative risks calculated against placebo or other comparator).

When a common, very common or serious adverse reaction (e.g. suicide) also occurs in the placebo group with a relevant frequency, both incidence rates can be stated to put the risk into perspective (e.g. in subsection c).

Adverse reactions from safety studies

The choice of the frequency category to which any adverse reaction will be assigned is based on the point estimate of the crude incidence rate derived from a study designed in such a way that specific adverse events occurring in patients within a defined observation period would have been detected and reasonably attributed to the medicinal product. In this situation, it is possible to calculate a point estimate of the crude incidence rate using standard statistical methods. In cases where the original information is expressed as an incidence density (denominator expressed as person-time), an appropriate transformation into an incidence proportion should be performed for choosing the frequency category. Normally, incidence proportions for the most representative exposure period (e.g. 1 week, 3 months, 1 year) should be used to derive the frequency category. However, this may not be appropriate if the hazard function increases over time; in this case, the adverse reaction and its frequency pattern, when clinically relevant, should be properly described in section c).

The frequency category to be chosen for each adverse reaction should not be based on differences calculated against a comparator. However, when data are derived from a study with a non-exposed group and the rate difference attributed to the medicinal product is smaller than the baseline or background incidence rate, and if the adverse reaction is considered important, the background incidence may be provided (e.g. in section c).

Adverse reactions from spontaneous reporting

The number of spontaneous reports should not be stated because the number can quickly become outdated. Frequencies based on reporting rates from a spontaneous reporting system should not be used to assign frequency category. In case of an unexpected adverse reaction detected from spontaneous reporting, each adequately designed study where this adverse reaction could have been detected should be reviewed to choose a frequency category. If the adverse reaction has never been observed in clinical trials, then the upper limit of the 95% confidence interval is not higher than 3/X, with X representing the total sample size summed up across all relevant clinical trials and studies (e.g. those with a follow-up long enough to detect the adverse reaction).

For example, if a particular adverse reaction has not been observed among 3600 subjects exposed to the product in clinical trials and studies, then the upper limit of the 95% confidence interval for the point estimate is 1/1200 or less and the frequency category should be "rare", based on worst value of the point estimate. The rationale for the frequency category for that particular reaction could be explained in sub-section c).

4.9 Overdose

Describe acute symptoms and signs and potential sequelae of different dose levels of the medicinalproduct based on all available information including accidental intake, mistakes and suicide attemptsby patients.

Taking into account all relevant evidence, describe management of overdose in man, e.g. in relation tomonitoring or use of specific agonists/antagonists, antidotes or methods to increase elimination of themedicinal product such as dialysis. However, there should not be any dosage recommendation of othermedicinal products (e.g. antidotes) as it could create conflict with the SmPCs of those other products.If applicable, counteractive measures based on genetic factors should be described.

Additional information on special populations
Information specifically observed in special populations such as elderly, patients with renalimpairment, patients with hepatic impairment, other concomitant diseases etc.

Paediatric population
If there are specific paediatric considerations, there should be a sub-section entitled 'paediatricpopulation'.

Special mention should be made of those medicinal products/strength of formulation for whichingestion of only one dose unit by children can cause fatal poisoning.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Sections 5.1 – 5.3 should normally mention information, which is relevant to the prescriber and to other health-care professionals, taking into account the approved therapeutic indication(s) and the potential adverse drug reactions. Statements should be brief and precise.

The sections should be updated regularly when new information becomes available, especially inrelation to the paediatric population.
5.1 Pharmacodynamic properties
Describe:

• Pharmacotherapeutic group and ATC code:

Inclusion of the therapeutic subgroup (2nd level of WHO classification) with the 3rdlevel (pharmacological subgroup) andthe 4th level (chemical subgroup) is recommended. If an ATC code is not yet available, this should be mentioned as 'not yet assigned'.

In case of medicinal product Authorized as similar biological medicinal product, the following statement will be included:
<<(Proprietary) Name> is a biosimilar medicinal product.

• Mechanism of action (if known)

• Pharmacodynamic effects.

• Clinical efficacy and safety

It may be appropriate to provide limited information, relevant to the prescriber, such as the main results (statistically compelling and clinically relevant) regarding pre-specified end points or clinical outcomes in the major trials, and giving the main characteristics of the patient population. Such information on clinical trials should be concise, clear, relevant and balanced, and should summarise evidence from relevant studies supporting the indication.
The magnitude of effects should be described using absolute figures. (Relative risks or odd ratio should not be presented without absolute figures).

In the exceptional cases when clinically relevant information from subgroup or post-hoc analyses is presented, it should be identified as such in a balanced manner reflecting the limited robustness of both positive and negative secondary observations.

Any relevant pharmacogenetic information from clinical studies may be mentioned here. This should include any data showing a difference in benefit or risk depending on a particular genotype or phenotype.

Paediatric population

The results of all pharmacodynamic (clinically relevant) or efficacy studies conducted in children should be presented under this sub-heading.

Information should be updated when new relevant information becomes available.

Results should be presented by age or relevant subsets.

When there are data available, but there is no Authorized paediatric indication, data should be presented and a cross-reference should always be made to section 4.2and, as appropriate to 4.3.

In presenting results of studies, particular attention should be given to include the relevant safety data. For exploratory studies, the results of the main endpoints should be given with the main characteristics of the population studied and the doses used. When they are available, information and results of confirmatory studies should usually supersede and replace those of exploratory studies. For confirmatory studies, the objectives, the study duration, the doses used (and the formulation used if different from the marketed one), the main characteristics of the patient population studied (including age and numbers of patient), and the main results regarding pre-specified endpoints should be provided, whether positive or negative. If data are considered inconclusive, this should be stated.

The objective and the main results or the conclusion of any specific clinical safety study should also be given.

5.2 Pharmacokinetic properties

Pharmacokinetic properties of the active substance(s) relevant for the advised dose, strength and the pharmaceutical formulation marketed should be given in this section. If these are not available, results obtained with other administration routes, other pharmaceutical forms or doses can be given as alternative.

Basic primary pharmacokinetic parameters, for instance bioavailability, clearance and half-life, should be given as mean values with a measure of variability.

Pharmacokinetics items, which could be included in this section when relevant, are given below.

a. General introduction, information about whether the medicinal product is a pro-drug or whether there are active metabolites, chirality, solubility, information on the population in which general pharmacokinetic data were obtained, etc.

b. General characteristics of the active substance(s) after administration of the medicinal product formulation to be marketed.

Absorption: complete or incomplete absorption; absolute and/or relative bioavailability; first pass effect; T_{max}; the influence of food; in case of locally applied medicinal product the systemic bioavailability; involvement of transport proteins. If available, information on the site of absorption in the gastro-intestinal tract should be stated (as it may be important for administration by enteral feeding tubes).

Distribution: plasma protein binding; apparent volume of distribution per kilogram bodyweight (l/kg); tissue and/or plasma concentrations; pronounced multi-compartment behaviour; involvement of transport proteins.

Biotransformation: degree of metabolism; which metabolites; activity of metabolites and contribution to effect and toxicity; enzymes involved in metabolism; site of metabolism; results from in vitro interaction studies that indicate whether the new compound can induce/inhibit metabolic enzymes.

Elimination: elimination half-lives, total clearance; inter and/or intra-subject variability in total clearance; excretion routes of the unchanged substance and the metabolites including the relative portion of the hepatic and renal eliminated fraction, involvement of transport proteins.

Linearity/non-linearity: linearity/non-linearity of the pharmacokinetics of the active substance with respect to dose and/or time; if the pharmacokinetics are nonlinear with respect to dose and/or time, the underlying reason for the non-linearity should be presented. Additional relevant information should be included here.

c. Characteristics in specific groups of subjects or patients

- Variations with respect to factors such as age, weight, gender, smoking status, polymorphic metabolism and concomitant pathological situations such as renal failure, hepatic disease, including degree of impairment. If the influence on pharmacokinetics is considered to be clinically relevant, it should be described here in quantitative terms (cross-reference to section 4.2 when applicable).

d. Pharmacokinetic/pharmacodynamics relationship(s)

- Relationship between dose/concentration/pharmacokinetic parameter and effect (either true endpoint, validated surrogate endpoint or side effect).
- The population studied should be described.

Paediatric population

Results of pharmacokinetic studies in the different paediatric age groups should be summarized, with comparison to adults if available. If appropriate, the dose producing similar product exposure as indults could be given. The pharmaceutical form(s) used for pharmacokinetic studies in children should be stated. Uncertainties due to limited experience should be stated.

5.3 Preclinical safety data

Information should be given on any findings in the non-clinical testing which could be of relevance for the prescriber, in recognizing the safety profile of the medicinal product used for the authorized indication(s), and which is not already included in other relevant sections of the SmPC.

If the results of the non-clinical studies do not add to the information needed by the prescriber, then the results (either positive or negative) need not be repeated in the SmPC.

The findings of the non-clinical testing should be described in brief with qualitative statements as outlined in the following example:

- Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.

- Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

- Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows.

Findings of non-clinical studies relevant for use in the paediatric population, including juvenile animals and peri-or post- natal studies, should be presented with a discussion of their clinical relevance, under a sub-heading if necessary.

<Environmental Risk Assessment (ERA)>

Where relevant, conclusions on the environmental risk assessment of the product should be included, with reference to section 6.6.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

A list should be given of the excipients, expressed qualitatively only. All excipients, which are present in the product, should be included, even those present in small amounts, such as printing inks. Further details on the excipients to be declared may be found in the section on definitions and examples in the *Guidelines on format and content of labels for medicinal products*

For transdermal patches, all ingredients of the patch (including the adhesive, release liner and backing film) should be mentioned.

The active substance itself, residues of substances used during manufacture of the finished product (for example, solvents, head-space gases or antibiotics in vaccine manufacture), lubricants for prefilled
syringes and constituents of capsule shells for inhalation powders not intended to be taken should not be included.

However, certain residues such as residues of antibiotic or other antimicrobial agents used in production that are known allergens with a potential for inducing undesirable effects should be mentioned in section 4.3 or 4.4 as appropriate.

Excipients should be referred to by their recommended INN if existing, accompanied by the salt or hydrate form if relevant or by their recognizes pharmacopoeial name. If an excipient has neither an INN nor a pharmacopoeia name, it should be described by its usual common name. References to the pharmacopoeial quality should not be included. E numbers should be given along with the common name of the excipient where they exist and when necessary for proper use, e.g. when the excipient is listed in the Guideline on the excipients in the label and package leaflet of medicinal products for human use (as having recognised action or effect).

The ingredients in excipient mixtures should be listed individually. In cases where the full composition of a flavour or fragrance is not known to the applicant or is too complex, it may be declared in general terms (e.g. ‘orange flavour’, ‘citrus perfume’). However, any of the components, which are known to have a recognised action or effect, should be included.

Ingredients that may or may not be added for the pH adjustment should be followed by the parenthesis ‘(for pH-adjustment)’

Proprietary names or general descriptive names such as ‘printing ink’ should not be used in place of the common name of an ingredient or of a mixture of ingredients but may be used in conjunction with the name(s) of the ingredient(s), so long as it is clear which ingredients are described by the name. Chemically modified excipients should be declared in such a way as to avoid confusion with the unmodified excipients, e.g. ‘pregelatinised starch’.

In the case of a product containing a covert marker for the purpose of tracking, tracing and authentication, a general term such as “authentication factor” should be included in the list of excipients instead of the name of the excipient, unless the excipient is one that is known to have a

recognised action or effect.

For clarity, it is recommended that each excipient be listed on a separate line. It can be useful to list excipients according to the different parts of the product, e.g. tablet core/coat, capsule contents/shells, etc. For products that are presented in more than one container or in dual-chamber containers, theexcipients should be listed per container or per chamber.

Abbreviations for excipients should not be used. However, where justified for space considerations, abbreviations for excipient names may appear on the labelling, on condition that these abbreviations
are designated in section 6.1.

6.2 Incompatibilities

Information on physical and chemical incompatibilities of the medicinal product with other products with which it is likely to be mixed or co-administered should be stated. This is particularly important for medicinal products to be reconstituted and/or diluted before parenteral administration. Significant interaction problems, e.g. sorption of products or product components to syringes, large volume parenteral containers, tubing, in-line filters, administration sets, etc. should be stated.

Statements concerning compatibility of the product with other medicinal products or devices should not be included in this section but in section 6.6. Statements concerning pharmacological and chemical/physical incompatibilities with food should be included in section 4.5. If appropriate, the standard statement, 'Not applicable', should be included.

For certain pharmaceutical forms, e.g. parenterals, either of the following standard statements should be included as appropriate:

• *'In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.'*

• *'This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.'*

6.3 Shelf life

The shelf life should be given for the medicinal product as packaged for sale and, if appropriate, after dilution or reconstitution or after first opening.
A clear statement of the shelf life should be given, in an appropriate unit of time.

An in-use shelf life may need to be stated for other medicinal products if developmentstudies have found it to be necessary.

Additionally, if different concentrations need to be prepared, e.g. for use in children, the physicochemical stability throughout the entire concentration range should be stated; e.g. *"The stability has been demonstrated between x mg/ml and y mg/ml for t hours/days at 25 ºC and 2-8 ºC"*.

In case of a paediatric indication, if no age appropriate formulation is available for children but an extemporaneous formulation could be prepared from an existing formulation, relevant physicochemical data on storage and stability should be included here with a cross-reference in
sections 6.4 and 6.6."
In case of specific temporary storage conditions need to be provided to healthcare professionals orpatients, e.g. for the purpose of ambulatory use (e.g. shelf-life 24 months at 2-8°C of which 3 months could be below 25°C), specific additional guidance should be provided as appropriate. Such information should always be based on stability data. In particular, the recommended temperature range and maximum duration of temporary storage should be specified. This guidance may also include the action to be taken after the product has been stored under the temporary storage conditions (e.g. discard immediately). Statements such as "These data are not recommendations for storage" should not be used.

No reference should be made to the container unless there are different shelf lives for different containers. Storage conditions should not be included, except for the storage conditions after opening (see the corresponding guideline). Statements such as 'Do not use after the expiry date' should not be included.

When a device is supplied together with a medicinal product, the in-use shelf-life of the device should be given where applicable.

6.4 Special precautions for storage

Storage warnings should be stated.

For storage of sterile products that have been opened, diluted or reconstituted, a cross-reference should be made to section 6.3.
Note that if a specific storage warning is required, the warning should be consistent between the SmPC, label and PIL.

A warning to keep the product out of the reach and sight of children should not be included in the
SmPC.

6.5 Nature and contents of container

Reference should be made to the immediate container using recognized pharmacopoeial standard term; the material of construction of the immediate container should be stated ('glass vials', 'PVC/Aluminium blisters', 'HDPE bottles'); and any other component of the product should be listed, e.g. needles, swabs, measuring spoons, syringes inhaler devices, desiccant. The graduation on measuring devices should be explained. The container of any solvent provided with the medicinal product should also be described. Excessive detail, e.g., concerning the colour of the stopper, the nature of the heat-seal lacquer, should usually not be included. For parenteral preparations, when enclosure colour is used to differentiate between the presentations of a product, this should be stated here.

If appropriate, it should be indicated if the container closure is child-resistant.

Examples on the text in this section:

'<Volume> ml suspension in a pre-filled syringe (glass) with plunger stopper (chlorobutylrubber) with or without needle in pack sizes of 5 or 10.'
'HDPE bottle with a child-resistant closure and a silica gel desiccant.Pack-sizes of 30, 60 or 90 film-coated tablets.'

All pack sizes should be listed. Pack sizes mentioned should include the number of units, number of doses (for e.g. multi-dose vaccines, inhalers, etc.), total weight or volume of the immediate container, as appropriate, and the number of containers present in any outer carton. If appropriate, a standard statement, 'Not all pack sizes may be marketed', should be included, in order to alert health professionals to the fact that not all listed pack sizes may be available for prescribing or dispensing.

Multiple unit packs for distribution purposes only do not constitute new pack sizes for marketing of the product and should therefore not be included in this section.

6.6 Special precautions for disposal <and other handling>

Instructions for disposal should be included here, if appropriate for the product.

Where special precautions for the handling and disposal of certain products such as cytotoxics and some biological products or waste material derived from it are advised, e.g. in the case of products containing live organisms, these should be stated in this section, as should, where relevant, the disposal of items which come into contact with the product, such as nappies, or spoons used to administer oral vaccines. If relevant, a cross-reference to conclusions on the environmental risk assessment described in section 5.3 can be included.

If applicable, e.g. for cytotoxics, the following standard statement should be included, 'Any unused product or waste material should be disposed of in accordance with local requirements.'

If there are no special use or handling instructions for the pharmacist or other healthcare professionals, the standard statement, 'No special requirements.' should be included.

Any directions necessary for the accurate preparation of certain products such as cytotoxics and some biological products and/or necessary for the protection of persons including parents or carers preparing or handling the product should be stated.

In section 4.2, instructions on handling of the product by the doctor, other health personnel, or patient should be included, as well as general information concerning the administration of the product (whether administered by the patient or the health personnel). If instructions for use/handling are needed where the medicinal product has to be prepared before use, e.g. where it must be suspended or diluted, this information has to be given here.
For clarity, a cross-reference in section 4.2 to the relevant information in section 6.6 could be included, e.g. 'For instructions on dilution of the product before administration, see section 6.6.'

It is recommend that only information necessary for the pharmacist or other health personnel to prepare the product for administration to the patient should be included here.

Information on the preparation (e.g. the suspension of a powder for injection, or preparing a dilution) of the medicinal should be included in section 6.6, regardless of who prepares the product (e.g. pharmacist, doctor, other health personnel, patient, parents or carers). In the case of products for reconstitution, the appearance of the product after reconstitution should be stated.

Statements concerning compatibility of the product with other medicinal products or devices can be given here provided the data have been provided in the dossier.

In the exceptional cases where a product is indicated in children and where no adequate paediatric formulation can be developed (based on duly justified scientific grounds), information on extemporaneous formulation should appear under a sub-heading "*Use in the paediatric population*" and should cross-refer to the section 4.2. Detailed instructions for the preparation of the extemporaneous formulation from the appropriate "adult" or other "older children" dosage form and additional information on extemporaneous formulations for use in younger children shall be provided and, where appropriate, the maximum storage time during which such preparation will conform to its specifications. When necessary, the required packaging material and storage conditions should be
stated here.

Any specific warnings for the handling of the product should be in section 4.4.

Information on risks due to occupational exposure should be included in this section, with reference to section 4.4 or 4.8 if there is information in that section.

7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESSES

Name and permanent address or registered place of business of the Marketing Authorization Holder and manufacturing site(s) physical address.

Telephone, fax numbers or e-mail addresses may be included (not websites or emails linking to websites).

8. MARKETING AUTHORIZATION NUMBER

Item to be completed by the Marketing Authorization Holder once the Marketing Authorization has been granted by ZFDA.

9. DATE OF FIRST <REGISTRATION> / RENEWAL OF THE <REGISTRATION>

Item to be completed by the Marketing Authorization Holder once the Marketing Authorization has been granted or renewed.

Both the date of first authorization and, if the authorization has been renewed, the date of the (last) renewal should be stated in the format given in the following example:

Date of first authorization: 3 April 1985
Date of latest renewal: 3 April 2000

10. DATE OF REVISION OF THE TEXT

Leave blank in case of a first Marketing Authorization.

11. DOSIMETRY (IF APPLICABLE)

Full details of internal radiation dosimetry should be included in this section for radiopharmaceuticals.
For all other products, this section should be excluded.

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

For radiopharmaceuticals, additional detailed instructions for extemporaneous preparation and quality control of such preparation and, where appropriate, maximum storage time during which any intermediate preparation such as an eluate or the ready-to-use pharmaceutical will conform to its specifications.

Special instructions relating to the disposal of containers and unused contents should also be included.

PART V:

ZFDA GUIDELINES ON FORMAT AND CONTENT OF LABELS FOR PHARMACEUTICAL PRODUCTS

1. GENERAL REQUIREMENTS

(a) The label text

Particulars in the label shall be easily legible, clearly comprehensible and indelible.

(b) Conformity with the Summary of Product Characteristics

The label text should be in conformity with the summary of products characteristics.

(c) Language

The labelling must be presented at least in English or Swahili and any other language as may be required by the EAC Partner State(s) where the product is placed on the market. If more than one language is used, then all of the text must be in each language and the overall readability should not be adversely affected. The content of all language versions must be identical. It is recommended to group different text elements for each language, where appropriate.

2. PARTICULARS TO BE INCLUDED ON THE LABEL

(a) Outer packaging or, where there is no outer packaging, on the immediate packaging

The label should include at least the following:

i. Proprietary Name where applicable
ii. International Non-Proprietary name(s) of the Active Pharmaceutical Ingredient(s)
iii. Amount of each Active Pharmaceutical Ingredient present in a dosage unit
iv. List of excipients known to be a safety concern for some patients, e.g. lactose, gluten, metabisulfites, parabens, ethanol, or tartrazine. For parenterals and topical preparations, all excipients should be listed.
v. Pharmaceutical form and contents of the container, e.g. number of dosage units, weight or volume.
vi. Method and route(s) of administration and the statement “Read the patient information leaflet before use.”
vii. Special warning that the medicinal product must be stored out of the reach and sight of children (“Keep out of the reach and sight of children”).
viii. Other special warnings and handling precautions, if necessary (e.g. in case of specific toxicity of the agents)
ix. The word “sterile” if the product is sterile
x. Batch number assigned by the manufacturer
xi. The manufacturing date
xii. The expiry date
xiii. Special storage conditions, if applicable
xiv. Special precautions for disposal of unused medicinal products or waste material derived from such medicinal products, if appropriate

xv. The name and address of the Marketing Authorization Holder
xvi. Physical address of the site responsible for release of the finished product
xvii. Advice on general classification for distribution, e.g., Controlled Medicines, Prescription Only Medicines, Pharmacy Only Medicines, Over-the-Counter and General Sales List
xviii. Instruction on use
xix. The proprietary name, strength and expiry date in braille (Marburg Medium)
xx. The registration number issued by ZFDA.

(b) Guidance for small containers

For containers of less than or equal to 10 ml capacity that are marketed in an outer pack such as a carton, and the outer pack bears all the required information, the immediate container should contain at least these minimum information (added):-

i. Brand Name of the FPP, INN name, strength, pharmaceutical form, active substance(s) and route(s) of administration
ii. Method of administration
iii. Batch number assigned by the manufacturer
iv. Expiry date
v. Manufacturing date if space is enough
vi. Contents by weight, by volume or by unit
vii. The name and address of the manufacturing site— or a logo that unambiguously identifies the company.
viii. Directions for use, and any warnings or precautions that may be necessary

(c) Guidance for Blisters and strips

Blisters and strips should include, as a minimum, the following information (printed directly):-

i. Name, strength and pharmaceutical form of the FPP.
ii. Name and physical address of the manufacturing site (the site responsible for release of the finished product)
iii. The batch number assigned by the manufacturer
iv. The expiry date [Note that for co-blistered products, the expiry date is that of the product which expires first.]
v. The manufacturing date, if space is enough
vi. The batch number assigned by the manufacturer
vii. Directions for use, and any warnings or precautions that may be necessary.

(d) Additional labelling information

ZFDA may require the use of certain forms of labelling making it possible to indicate:-

i. Identification and authenticity;
ii. A statement that the product is a property of government

The information should be accommodated on the label in a box, to appear on one side of the pack.

3. CONTROL OF THE CONFORMITY OF THE LABELLING

The labelling of the medicinal product forms part of the authorization and it must, therefore, be approved by the ZFDA when the authorization is granted.

4. CHANGES TO THE LABELLING

Any changes to the labelling, which are not connected with the Summary of Product Characteristics, shall be notified to ZFDA where the authorization is granted. Therefore, if a Marketing Authorization Holder wishes either to introduce any label text additional to that in the decision or to change any aspect of the labelling he must first notify this change to ZFDA. ZFDA shall inform the Marketing Authorization Holder whether the proposed change is accepted or not.

PART VI:

ZFDA GUIDELINES ON FORMAT AND CONTENT OF PATIENT INFORMATION LEAFLET FOR PHARMACEUTICAL PRODUCTS

1. GENERAL REQUIREMENTS

(a) The patient information leaflet text

Particulars in the patient information leaflet shall be easily legible, clearly comprehensible and indelible.

(b) Conformity with the Summary of Product Characteristics

The patient information leaflet text should be in conformity with the summary of products characteristics.

(c) Language

The patient information leaflet must be presented at least in English or Swahili and any other language as may be required by the EAC Partner State(s) where the product is placed on the market. If more than one language is used, then all of the text must be in each language and the overall readability should not be adversely affected. The content of all language versions must be identical. It is recommended to group different text elements for each language, where appropriate.

2. PARTICULARS TO BE INCLUDED ON THE PATIENT INFORMATION LEAFLET

The patient information leaflet shall include the particulars outlined in the template in the following section.

The applicant should complete the template and delete the parts which are not applicable.

3. TEMPLATE FOR PATIENT INFORMATION LEAFLET

{(Proprietary) name strength pharmaceutical form}[2]
{Active substance(s)}

Read all of this leaflet carefully before you start <taking><using> this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your <doctor, health care provider><or><pharmacist>.

- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your <doctor, health care provider><or><pharmacist>.>

In this leaflet:

[Delete sections that are not applicable]

a) WHAT {PRODUCT NAME} IS AND WHAT IT IS USED FOR

b) BEFORE YOU <TAKE><USE> {PRODUCT NAME}

Do not <take><use> {product name}
- <if you are allergic (hypersensitive) to {active substance(s)} or any of the other ingredients of {product name}.>
- <if ...>

Take special care with {product name}
- <if you ...>
- <when ...>
- <Before treatment with {product name},...>

<Taking><Using> other medicines
<Please tell your <doctor, health care provider><or><pharmacist> if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.>

<Taking><Using> {product name} with food and drink

Pregnancy and breast-feeding

<Ask your <doctor, health care provider><or><pharmacist> for advice before taking any medicine.>

Driving and using machines

<Do not drive <because...>.>
<Do not use any tools or machines.>

Important information about some of the ingredients of {product name}

c) HOW TO <TAKE><USE> {PRODUCT NAME}

<Always <take><use> {product name} exactly as your doctor or health care provider has told you. You should check with your <doctor, health care provider><or><pharmacist> if you are not sure.><The usual dose is...>

<Use in children>

If you <take><use> more {product name} than you should

If you forget to <take><use> {product name}

<Do not take a double dose to make up for a forgotten <tablet><dose><…>.>

If you stop <taking><using> {product name}

<If you have any further questions on the use of this product, ask your <doctor, health care provider><or><pharmacist>.>

d) POSSIBLE SIDE EFFECTS

Like all medicines, {product name} can cause side effects, although not everybody gets them.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your <doctor, health care provider><or><pharmacist>.

e) HOW TO STORE {PRODUCT NAME}

Keep out of the reach and sight of children.

<Do not store above ºC>, <Store in the original <container><carton>>

Do not use {product name} after the expiry date which is stated on the <label><carton><bottle><...><after {abbreviation used for expiry date}.><The expiry date refers to the last day of that month.>
<Do not use {product name} if you notice {description of the visible signs of deterioration}.
<Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.>

f) FURTHER INFORMATION

What {product name} contains

- The active substance(s) is (are)…
- The other ingredient(s) is (are)…

What {product name} looks like and contents of the pack

Name and full physical address of Marketing Authorization Holderand Manufacturing site

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

For any information about this medicinal product, please contact the <local representative of the> supplier:

{Country}
{Name}
<{Address}
B-0000 {City}>
tel: + {telephone number}
<{e-mail}>

{Country}
{Name}
<{Address}
B-0000 {City}>
tel: + {telephone number}
<{e-mail}>

<as appropriate, add additional local representatives to the above table>

This leaflet was last approved in {MM/YYYY}.

PART VII:

ZFDA COMMON GLOSSARY OF TERMS USED IN MEDICINES REGISTRATION

ABBREVIATIONS AND ACRONYMS

BMGF	-	Bill and Melinda Gates Foundation
EAC	-	East African Community
EAC-MRH	-	East African Community Medicines Regulatory
EMA	-	European Medicines Agency
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
MER	-	Medicines Evaluation and Registration
NEPAD	-	New Partnership for African Development
NMRA	-	National Medicines Regulatory Authority
		Requirements for Registration of Pharmaceuticals for Human Use
TWG	-	Technical Working Group
US FDA	-	United States Food and Drug Administration
WHO	-	World Health Organization
ZFDA	-	Zanzibar Food and Drug Agency

2. INTRODUCTION

Glossary of terms in medicines registration have 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 guidelines on application for registration of medicines from respective EAC Partner States. Also, the terms were 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, wide spread use and consultation from EAC National Medicines Regulatory Authorities.

3. SCOPE

This glossary of terms primarily addresses terms that are used in various ZFDA guidelines on registration of human medicinal products.

4. GLOSSARY

In the context of ZFDA-Human Medicines 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 Pharmaceutical Ingredient Master File-(APIMF)	See Drug Master File (DMF)
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]*
Registrant	*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)*
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).*
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)*
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	Direct-to-consumer advertising (DTC advertising)

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. Currently we have Prescription Only Medicines (POM) and Over the Counter (OTC).*(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 Substance	See Active pharmaceutical ingredient (API)
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).*
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).
Forensic category	See Distribution category
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]*
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)*
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	Is a person who holds authorization to place a medicinal product in Zanzibar and is responsible for that product.
Marketing Authorization(MA)	Means approval to market a medicinal product in Zanzibar (*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 instrument apparatus, laboratory equipment and reagents, implement, machine, appliance implant, in vitro reagent or calibrator, software, material or other similar or related article which: (a) is intended by manufacturer to be used, alone or in combination for human being or other animals for one more of the specific purpose(s) of: (i) diagnosis, prevention, monitoring, treatment or alleviation of diseases or compensation for an injury; (ii) investigation, replacement, modification or support or the anatomy or of a physiological process; (iii) supporting or sustaining life; (iv) control of conception; (v) disinfection of medical devices; (vi) providing information for medical diagnostic purposes by means of in vitro examination or specimens derived from the human body or other animal; and (b) does not achieve its primary intended action in or an the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means; "Medical device family" means a group of medical devices that are

	made by the same manufacturer, that differ only in shape, color, flavor or size, that have the same design and manufacturing process and that have the same intended use;
Medicinal Product	See Pharmaceutical product
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 product/originator brand	An originator brand is generally the product that was first authorized worldwide for marketing (normally as a patented product) on the basis of 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).*
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).*
Summary of Product Characteristics (SmPC)	Product information as approved by the Regulatory Authority. The SPC 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)*
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 VIII:

LIST OF STANDARD TERMS FOR PHARMACEUTICAL DOSAGE FORMS AND ROUTES OF ADMINISTRATION

ABBREVIATIONS AND ACRONYMS

CTD - Common Technical Document

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

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.

1.2.1 Definitions

For the purposes of the Standard Terms, the following definitions apply.

1.2.1.1 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.

1.2.1.2 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

1.2.1.3 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.

1.2.2 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.

1.2.3 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'.

1.2.4 Procedure for the addition or modification of terms in the list of standard terms

1.3 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	ENDOTRACHEOPULMONARY

INSTILLATION, POWDER AND SOLVENT FOR SOLUTION	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

1.4 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

2. 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 IX:

ZFDA GUIDELINES ON REGISTRATION OF FIXED DOSE COMBINATION PHARMACEUTICAL PRODUCTS

Abbreviations

AIHW	Australian Institute of Health and Welfare
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)
SPC	Summary of Product Characteristics (*see* Glossary)
TGA	Therapeutic Goods Administration
WHO	World Health Organization

1. Scope

1.1 The scope of these guidelines is covers prescription and non-prescription medicines.

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.

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.

1.2 The principles in these guidelines would also apply to chemical combinations and complexes that comprise more than one active.

1.3 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 ZFDA 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 actives.

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

- The new FDC-FPP combines actives that are of established safety and efficacy but have not previously been used in combination for this indication.
- 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 in the ZFDA guidelines on submission of documentation for registration of human pharmaceutical products.

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	√	√	√	√
Bioavailability data[a]	Not usually	Not usually	Sometimes	√
Bioequivalence data	√	√	Sometimes	Sometimes
Preclinical	Not usually	Not usually	Sometimes	√

Requirement	Scenario 1	Scenario 2	Scenario 3	Scenario 4
pharmacology and safety				
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	√	√

6.1.6 A full quality data set is required in all scenarios (see 6.3 below).

6.1.7 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.

6.1.8 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.

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 pharmacopoeial monographs, WHO guidelines, ICH guidelines and ZFDA 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 ZFDA guidelines on submission of documentation for registration of human medicinal products.

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)

6.5.9 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.

6.5.9.1 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.

6.5.9.2 Data from microbiological preclinical studies of FDCs are particularly useful when clinical trials of monotherapy are inappropriate or unethical.

6.5.9.3 Data from the following types of study should normally be available for the combination:

6.5.9.3.1 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.

6.5.9.3.2 Characterization of microbiological activity in appropriate animal models of infection with the targeted pathogen(s).

6.5.9.3.3 If possible, characterization of the mechanism by which the actives exhibit additive or synergistic microbiological activity against the targeted pathogen(s).

6.5.9.3.4 The potential for antagonistic effects between the actives.

6.5.9.3.5 The potential for development of resistance by target pathogens.

6.6 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.

6.6.1 General principles

6.6.1.1 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.

6.6.1.2 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.

6.6.1.3 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.

6.6.1.4 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.

6.6.1.5 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:

6.6.1.5.1 Historical clinical data, preferably at an exposure comparable to that for the proposed FDC.

6.6.1.5.2 Bridging pharmacokinetic data.

6.6.1.5.3 Preclinical pharmacology and/or toxicology data.

6.6.1.5.4 In vitro data (e.g. microbiological studies).

6.6.1.6 If the FDC is available in more than one strength or ratio of doses, there should be a risk–benefit assessment for each combination.

6.6.1.7 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.

6.6.1.8 If the combination is intended for long-term use, data on safety in patients will normally be required for 6 months or longer.

6.6.1.9 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.

6.6.1.10 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.

6.6.1.11 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.

6.6.1.12 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.

6.6.1.13 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.

6.6.1.14 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.

6.6.1.15 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.

6.6.1.16 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”.

6.6.1.17 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).

6.6.2 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.

6.6.2.1 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:-

6.6.2.1.1 Ritonavir boosts the activity of protease inhibitors.

6.6.2.1.2 Carbidopa and benserazide both reduce decarboxylation of levodopa in the gut wall, and consequently reduce the dose of levodopa that should be administered.

6.6.2.1.3 Clavulanic acid reduces bacterial hydrolysis of beta lactam antibiotics and consequently both increases the concentration and prolongs the duration of effectiveness.

6.6.2.2 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.

6.6.2.3 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.

6.6.3 Additional guidelines for scenario 3

6.6.3.1 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.

6.6.3.2 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.

6.6.4 Additional guidelines for scenario 4

6.6.4.1 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.

6.6.4.2 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.

6.6.4.3 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*).

6.6.5 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.

6.6.5.1 In the context of FDCs, equivalence trials are largely confined to bioequivalence studies.

6.6.5.2 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.

6.6.5.3 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:

6.6.5.3.1 The treatment whose risk–benefit profile is best supported by evidence or is at least well established.

6.6.5.3.2 One or more of the actives in the FDC given as a single treatment.

6.6.5.3.3 A placebo.

6.6.5.4 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.

6.6.6 Paediatric dosage forms

6.6.6.1 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

6.6.6.2 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

6.6.6.3 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.

6.6.6.4 The pharmacokinetic profile of each active should be established in the age groups for which the FDC is indicated.

6.6.6.5 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.

6.6.6.6 When defining target plasma concentrations in the paediatric population, possible differences in the concentration–effect relationship should be taken into account.

6.6.6.7 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 ZFDA 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

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.

1. 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.

2. 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).

3. 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.

4. 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 X:

ZFDA GUIDELINES ON PROCEDURAL ASPECTS FOR APPLICATIONS FOR MARKETING AUTHORIZATION OF PHARMACEUTICAL PRODUCTS

ABBREVIATIONS AND ACRONYMS

BMGF	-	Bill and Melinda Gates Foundation
BMR	-	Batch Manufacturing Record
EAC	-	East African Community
EAC-MRH	-	East African Community Medicines Regulatory Harmonization
EMA	-	European Pharmaceutical products Agency
FEAPM	-	Federation of East African Pharmaceutical Manufacturers Harmonization
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
MER	-	Medicines Evaluation and Registration
NEPAD	-	New Partnership for African Development
NMRA	-	National Medicines Regulatory Authority
TWG	-	Technical Working Group
WHO	-	World Health Organization

1. INTRODUCTION

ZFDA issues marketing authorization of all pharmaceutical products for human use prior to their use in the Zanzibar. The objective of pharmaceutical product marketing authorization is to ensure that pharmaceutical products marketed in Zanzibar are safe, efficacious and of good quality and are manufactured in facilities that complies with the requirements prescribed in the ZFDA Good Manufacturing Practice guidelines. All local manufacturers, wholesalers, distributors and importers of pharmaceutical products must be licensed before they can conduct their businesses.

The guideline covers the steps that are followed from the submission of a dossier to the final outcome, the timeframe and procedure for competent authorities to amend, where necessary the conditions of marketing authorization of a particular product.

2. SCOPE

The guideline is applicable for all types of application submitted to the ZFDA that include new application, renewal of application and application for variation of a registered pharmaceutical product.

3. TYPES OF APPLICATIONS

3.1 For purposes of submission to ZFDA, applications are classified into new application, Application for Variation of a registered pharmaceutical product and renewal 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. GENERAL REQUIREMENTS AND APPLICATION PROCEDURES FOR PHARMACEUTICAL PRODUCT REGISTRATION

4.1 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.

4.2 The responsibility of applying for product marketing authorization rests with the company responsible for the introduction of the product into the Zanzibar market, i.e.: the Marketing Authorization Holder (MAH).

4.3 Applications must be duly completed and supported by all of the required documents i.e. Module I to Module V in accordance with ZFDA Common Technical Document (CTD) for registration of pharmaceutical products. The

submitted application will be screened for completeness within 30 working days. Dossiers which are incomplete will not be accepted for evaluation.

4.4 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.

4.5 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 ZFDA.

4.6 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.

4.7 Application must be accompanied by three samples of the commercial pack to enable full specifications analysis, when its necessary the Agency shall request more samples.

4.8 The applicant shall be required to pay the processing fee as per prescribed in the respective ZFDA fees and charges regulation, the fee must be paid to ZFDA bank account at the point of submission of the application.

5. 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 ZFDA 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 and asked to come and collect the dossier.

5.4 In case of a positive outcome during screening, ZFDA 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, ZFDA may request for further information and additional supporting documents from the applicant. Applicant should make available such information or documentation required for each correspondence within 180 days from the date of the request.

5.9 If no response is received from applicant after the 180 days, the clock stops and the application will be rejected/closed. A new application will have to be submitted if the MAH wishes to pursue marketing authorization of the product.

5.10 Evaluation of the additional information shall be carried out within 3 months from receiving such information.

5.11 The MAH will be informed of the decision of ZFDA in writing as to whether the application has been approved or rejected.

5.12 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.

5.13 For a product to be issued MA, it must be manufactured in a GMP compliant facility and studies conducted following GCP.

6. 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 ZFDA may require in relation to the registered product.

6.1.3 No change in name, composition, characteristics, origin, specifications, and manufacturer, and packing, indications, labelling, package insert, product literature or any other Particulars of the registered product shall be made without prior approval from ZFDA

6.1.4 The marketing authorization number must be:

- printed on the immediate and secondary container / packaging and immediate outer container/packaging and on the leaflet;
- printed in an indelible manner;
- NOT handwritten;

6.1.5 The labels for the registered product must comply with all of the labelling requirements as specified by the guidelines for labelling.

6.1.6 The registered product must only be indicated for use as approved by the ZFDA.

6.1.7 The holder of the marketing authorization certificate must inform ZFDA 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.

6.1.8 The holder of the registration certificate must notify in writing to ZFDA 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 ZFDA.

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 by ZFDA.

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:

i. Duly filled in application form for registration.

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

iii. Details of all changes during validity of the registration.

iv. Application must be accompanied by three samples of the commercial pack to enable full specifications analysis, when its necessary the Agency shall request more samples.

v. A site master file that describes the manufacturing facilities.

vi. Non-refundable evaluation fee for registration of pharmaceutical product and GMP and GCP inspection fees for facilities not inspected and approved by ZFDA within a period specified by ZFDA.

7. CANCELLATION OR SUSPENSION OF MARKETING AUTHORIZATION

7.1 ZFDA 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 ZFDA the marketing authorization certificate upon cancellation or suspension of marketing authorization of the product.

7.3 ZFDA shall notify all Partner States on the decision taken by the respective NMRA.

8. APPEALS AGAINST ZFDA DECISIONS ON PHARMACEUTICAL PRODUCT MARKETING AUTHORIZATION

8.1 For products that have been suspended and cancelled marketing authorization by ZFDA, MAH may make a written appeal to review its decision.

8.2 All notice of appeals must be made within thirty (30) calendar days from the date of ZFDA 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‘s dossier. Any additional or new information that was not earlier submitted will not be accepted. ZFDA may review or uphold its earlier decision.

8.4 If a person is dissatisfied with the decision after review, he may appeal to the Minister whose decision shall be final.

9. VARIATIONS IN PARTICULARS OF REGISTERED PRODUCTS

All variations to a registered product shall be made according to requirements stipulated in the ZFDA Application Guidelines for Variation of Registered Pharmaceutical Products.

PART XI:

ZFDA EVALUATION GUIDELINES FOR MARKETING AUTHORIZATION OF PHARMACEUTICAL PRODUCT DOSSIERS

For internal use only not to be printed as part of compendium

ABBREVIATIONS AND ACRONYMS

API	-	Active Pharmaceutical Ingredient
BCS	-	Biopharmaceutical Classification System
BMGF	-	Bill and Melinda Gates Foundation
CAS	-	Chemical Abstracts Service
CEP	-	Certificate of Suitability of the European Pharmacopoeia
CPP	-	Certificate of Pharmaceutical Product
CTD	-	Common Technical Document
DMF	-	Drug Master File
EAC-APIMF Master	-	East African Community Active Pharmaceutical Ingredient File
EAC-MRH	-	East African Community Medicines Regulatory Harmonization
FPP	-	Finished Pharmaceutical Product
GMP	-	Good Manufacturing Practice
IUPAC	-	International Union of Pure and Applied Chemistry
IVIVC	-	In Vitro In Vivo Correlation
MER	-	Medicines Evaluation and Registration
NCE	-	New Chemical Entity
NEPAD	-	New Partnership for Africa's Development
NMRA	-	National Medicines Regulatory Authority
OMP	-	Orphan Medicinal Product
PD	-	Product Dossier
PICS	-	Pharmaceutical Inspection Cooperation Scheme
PIL	-	Patient Information Leaflet
SPC	-	Summary of Product Characteristics
TWG	-	Technical Working Group
WHO	-	World Health Organization

1. GENERAL GUIDANCE ON EVALUATION OF MEDICINAL PRODUCT DOSSIER

This guideline is intended to guide evaluators and auditors of medicinal product dossiers to effectively evaluate the data provided in the submissions. Dossier evaluation is an objective, scientific, written analysis of information relevant to registration of a product. It provides an account of all necessary points, in summary, of studies and findings related to efficacy, safety and quality. It documents both the applicant's and evaluator's evidence-based findings, as well as the decisions taken regarding the dossier.

The objective of evaluation is to ensure that before a medicine is placed on the market there is enough evidence that it has been properly formulated, manufactured and adequately tested and meets the criteria of safety, efficacy and quality and there are adequate directions for and that there are systems in place to ensure consistent quality.

A medicinal product application dossier consists of information on general and technical data as follows:

- General information, which consists of introduction and administrative data.
- Technical data on quality of active pharmaceutical ingredient (API) and finished pharmaceutical product (FPP), which consists of chemistry, manufacturing, specifications and stability.
- Clinical data consisting of safety and efficacy data (pre-clinical and clinical studies data) for innovator product.
- Therapeutic equivalence data in lieu of safety and efficacy data for generic product.
- Labelling consisting of label and package inserts information.

The first step in the evaluation process is to screen the dossier to determine whether it complies with the application requirements (expand more on screening). This will prevent loss of valuable evaluation time, should product file(s) be incomplete in terms of data on quality, safety and efficacy.

If the file is complete, evaluator should consider the following aspects in the evaluation report:

1. The report should be sufficiently detailed to allow for secondary evaluation by other evaluators/experts in absence of the dossier.
2. In case the product is queried, the report should describe salient findings and those deficiencies that justify the queries intended for the applicant. These queries will be listed in the "list of query" at the end of evaluation report.

3. Cross-references should be used to clearly indicate the origin of any information used in the report, such as the specific parts of the dossier (e.g. overview, summary, and study reports), references to the literature or other sources.

4. The use of tables is encouraged; examples are given in the templates and are to be used as appropriate. Tables taken from the dossier may also be appended to the evaluation report.

5. It is recommended that the font used in the main text be Bookman Old Style, size 12. Text should not be italicized unless it is a binomial name.

2. GUIDELINES ON EVALUATION OF MEDICNAL PRODUCT DOSSIER AS PER EVALUATION TEMPLATE

2.1 INTRODUCTION AND ADMINISTRATIVE INFORMATION

2.1.1 INTRODUCTION

Give general background of the product on the following aspects:-

a) Brief description of the product type and whether the product is a generic product or innovator product (active substance {e.g. NCE, known chemical active substances, Biotech/Biological) radiopharmaceutical, herbal}, pharmaceutical form, container).

b) Highlight if a paediatric formulation was developed.

c) Orphan Medicinal Product (OMP) status, if relevant.

d) Mention indications, target population, posology (with regard to the ability of the product to deliver this posology, e.g. scored tablets), method of administration (if unusual, e.g. using a device).

e) Linked or related applications (e.g. drug of a pro-drug, line-extension, simultaneous or 'double' applications).

The information provided here is intended to provide a brief description of the main critical features of the product. The amount of information provided will depend on the nature of the particular product. The clinical context of use should also be briefly mentioned.

2.1.2 ADMINISTRATIVE INFORMATION

a) Complete administrative information as required in the evaluation template. Compare the particulars of the product, applicant and Finished Pharmaceutical Product (FPP) manufacturer on the application form, Certificate of Pharmaceutical Product (CPP), label and the database. Check

for concurrence of the particulars from the mentioned sources and give your comments.

b) Comment on Good Manufacturing Practice (GMP) status of the FPP manufacturer. If the FPP manufacturer is non-GMP compliant as per EAC GMP requirements, end evaluation by providing your overall conclusion and recommend the product for rejection citing non-GMP compliance as the reason for rejection and attach the relevant refusal letter to be communicated to the applicant. If the site is not yet inspected by EAC, raise a communication to the inspectors concerned with GMP inspection. If the FPP manufacturer is GMP compliant as per ZFDA GMP requirements, continue with evaluation as required.

c) Check and confirm if the FPP is registered in any of the countries recognized by EAC Partner States to have effective medicines regulation or elsewhere and comment whether evaluation follows full or abbreviated procedure. Information on registration status can be obtained from the application form and Certificate of Pharmaceutical Product (CPP) submitted in the dossier.

d) The following conditions must be fulfilled for abbreviated evaluation:-

   i. The FPP must be on the market in the country of origin; if not raise a query.

   ii. The submitted FPP composition should be identical (qualitatively and quantitatively) with the approved product and the Summary of Product Characteristics (SPC) should be comparable to the approved SPC in the country of origin.

   iii. The submitted FPP must be manufactured in the same facilities as the approved product.

e) If conditions outlined under (c) are fulfilled, continue with evaluation using abbreviated evaluation template.

f) If conditions outlined under (c) are not fulfilled, carry out full evaluation using full evaluation template.

NB: Certificate of Pharmaceutical Product must be original and specific to EAC Partner States where the product is intended to be marketed. It must be accompanied by full qualitative and quantitative formula of the product showing the names of all active and inactive ingredients, function, quantity per dosage unit e.g. mg/tablet, mg/5ml, etc. and percentage by w/w, v/v, etc and approved SPC.

Evaluation guidelines should be in line with CTD module

3. ACTIVE PHARMACEUTICAL INGREDIENT (CTD MODULE 3.2.S)

Note which option the active pharmaceutical ingredient's (API) information is presented and consult the guidelines and other references on the requirements for each option.

Option 1: Submission of Certificate of suitability of the European Pharmacopoeia (CEP)

Check if:-

- It is valid.
- There is a commitment in case of CEP withdrawal.
- A copy of the most current CEP (with annexes) is provided.
- There is declaration of access by the CEP holder.
- Summaries of the relevant information under the appropriate sections (e.g. S.1.3, S.3.1, S.4.1 through S.4.4, S.6 and S.7; have been provided.
- Provide your overall comment on this option and raise a communication to GMP inspectors in case of any deficiency.

Option 2: Submission of evidence for WHO pre-qualified API

Check if: -

- The API is prequalified by confirm with WHO website and/or evidence provided in the dossier. If prequalified; do not evaluate API information;
- Provide your overall comment on this option.

Option 3: Submission of ZFDA Active Pharmaceutical Ingredient Master File (ZFDA-APIMF) or Drug Master File (DMF).

Check if: -

- A valid ZFDA-APIMF or DMF exists. If YES; do not evaluate API information;
- Provide your overall comment on this option and raise a communication to GMP inspectors in case of any deficiency.
- If no valid DMF exists; carry out evaluation as required in the CTD.

Option 4: Full details in the Product Dossier (PD)

Check if signed declaration from API manufacturer has been submitted. If not, raise a query to the applicant to submit this information.

Carry out evaluation of the API as required in the evaluation template below:-

3.1 **Nomenclature and properties of API (S3.1-3.2)**

a) Give at least one sentence to mention the name and confirm whether the name is INN, or common name, etc.

b) State the IUPAC chemical name, CAS registry etc.

c) Include chemical structure; if applicable.

d) Indicate crucial properties and give values, e.g., pKa, solubility, etc. where relevant.

e) Mention if the active substance is present as a different salt, ester, complex, etc. than the active substance in the reference product.

Evaluate if submitted information under each part is correct and adequate as compared to the relevant official monograph or literature.

3.2 **Route of synthesis and specifications of the API(s) (S3.3-3.5)**

a) Note down the sites of manufacture of APIs and comment on whether they comply with GMP. Look for evidence of such compliance such as GMP certificate issued by a regulatory authority known to EAC Partner States to have efficient regulatory systems such as members of Pharmaceutical Inspection Cooperation Scheme (PICS) e.t.c.

b) Carefully go through and give comments on starting materials, each stage of synthesis, intermediates, solvents, catalysts, operating conditions and precautions, equipment used, isolation, and final purification of active ingredient and the flow diagram of the whole synthetic process

c) Check and confirm acceptance criteria for parameters declared by the applicant in the API specification document (for compendial APIs) and comment if they are comparable or not. Attach final API specification document in the evaluation report. For non-compendial APIs, comment if the acceptance criteria have been justified or if not raise a query to the applicant.

Evaluation should include critical statements on the adequacy of the description of the synthesis, of the control of the materials and intermediates, tests and limits for the API, justification for the limits, and reproducibility of the manufacturing process identifying those issues not adequately covered and which need to be addressed.

3.3 **Container closure system (S3.6)**

Evaluation of this part should enable to answer the following questions: -

a) Is the choice of the container/closure justified, bearing in mind the physical/chemical properties of the drug substance?

b) Does it provide adequate protection from microbial contamination, if this is considered to be necessary?

Confirm that the containers proposed for routine storage are those, which have been used in the stability studies supporting the re-test period (ref. S.3.7).

3.4 **Stability testing (S3.7)**

a) State if the studies were carried out in accordance with ZFDA requirements for stability testing of APIs. Are there any deviations? Are the deviations justified?

b) Discuss the relevance of the protocol, particularly with regard to the parameters tested in the studies.

c) Confirm that the analytical methods are stability - indicating. Stability indicating tests should be chosen, which are able to detect significant changes in the quality of the product.

d) Confirm that the containers used in the stability studies are the same as those proposed for routine storage (S.3.6).
e) Check if results are provided in numerical figures for quantifiable limit tests.

f) Summarize your observations and give your final conclusion on whether or not the proposed re-test period is justified.

4. FINISHED PHARMACEUTICAL PRODUCT [FPP]

4.1 Descriptions, Composition and Pharmaceutical DevelopmentP 4.2-3)

a) Give a detailed description of the drug product and its composition as provided in the dossier. Evaluate whether the description of the product in the dossier matches the sample, which has been submitted. Write down your evaluation.

b) Fill in the table active pharmaceutical ingredient(s) and all excipients with their specifications, amounts per dosage unit, amount per typical batch and function for each ingredient. Take note on any overage(s) in the formulation. Critically examine the functions of each ingredient in relation to the declared quantities and check whether they are within acceptable limits. The qualitative and quantitative composition of a generic may be different to the reference product. Evaluation should mention the observed differences and justification for such differences.

c) Go through formulation development report. Depending on type of dosage form, check whether formulation development is based on sound scientific principles. The report should cover compatibility studies conducted, justification for the choice and amount of each excipients used in the medicinal product, justification for overage if applicable, development of the dissolution test method if applicable, justification for differences from reference product in case of generic medicines, suitability and choice of container closure system, stability, demonstration of discriminatory properties of a given method and results of studies to establish In Vitro In Vivo Correlation (IVIVC), if relevant. Summarize your observations and comment whether pharmaceutical development report is adequate to establish the quality of the FPP and manufacturing process is under control to provide assurance on the quality consistency from batch to batch.

4.2 Manufacturing Procedure (P4.5-7)

Study the manufacturing procedures:

a) Description of manufacturing process and process controls: Flow diagram (incorporate it if possible, rather than present in an Annex) with indication of the critical steps.

b) Where the product consists of the active substance without excipients details of the manufacturers should also be referred to here and should be accordingly licensed.

c) Where ranges of batch size are proposed for production, blending of batches or the use of sub batches, the acceptability should be addressed.

d) The evaluator should discuss any specialized processes that may need to be inspected and raise a communication to GMP inspectors.

e) Confirm that process holding times and transport arrangements are relevant and have been justified.

f) The evaluator should comment here on whether process validation data are needed in the dossier (i.e. whether it is needed prior to authorization). Where non-standard methods are used these validation data would normally be expected.

4.3 **Specifications for excipients S4.8)**

Evaluate whether specifications for each excipients are adequate. Evaluation of 'new' excipients should be treated as new active substances and data requirements are 'full', i.e. manufacture and control, reference to toxicology studies, etc. (Detailed evaluation of these special new excipients should be discussed.

Compare certificates of analysis provided by respective excipients manufacturers with certificates of analysis provided by FPP manufacturer. Provide your evaluation on adequacy of tests and results.

4.4 **Control of the finished product (S4.9)**

a) Evaluate whether release and shelf life specifications have been presented side by side in tabular form, with brief reference to the method used. The product must comply with general requirements for a particular dosage form as provided in pharmacopoeia and product specific requirements. Specification summary, important tests, particularly relating to bioavailability/efficacy (e.g. dissolution, particle size, polymorphism if relevant.) and safety (impurities or sterility, pyrogens etc. for sterile products). The general relevance of the release specification should be discussed considering the method of manufacture and clinical use, route of administration etc.

b) Critically examine the tests prescribed and comment about their relevancy and compatibility with the type of formulation or dosage form.

c) Study the analytical test procedures and determine their applicability and validity for the product and validation data for their appropriateness for the intended use.

d) Examine batch analysis results including their authentication. Results of batch analysis must include results for all test specifications at the time of release.

e) Attach final FPP specification in the evaluation report.

4.5 **Container-closure system(s) S4.10)**

Evaluation of this part should enable to answer the following questions: -

a) Is the choice of the container/closure justified, bearing in mind the physical/chemical properties of the drug substance?

b) Does it provide adequate protection from microbial contamination, if this is considered to be necessary?

Confirm that the containers proposed for routine storage are those, which have been used in the stability studies supporting the re-test period (ref. S.4.11).

4.6 **Stability testing (S4.11)**

a) State if the studies are carried out in accordance with EAC requirements. If not, recommend the product for rejection. Are there deviations? Are the deviations justified?

b) Discuss the relevance of the protocol, particularly with regard to the parameters tested in the studies. Check whether bracketing and matrixing designs are acceptable.

c) Check whether the methods used are the same as or different to those described in S.4.9. Evaluate if methods are well validated and shown to be stability indicating.

d) Confirm that the containers used in the stability studies are the same as those proposed for routine storage.

e) Check if results are provided in numerical figures for quantifiable limit tests.

f) Summarize your observations and give your final conclusion on whether or not the proposed shelf life period is justified

In–Use stability:

Comment also on stability after opening and during use, e.g. for infusions to be diluted, stability after dilution and during administration, compatibility with commercially available administration equipment, etc. Evaluate data if in use shelf life and storage conditions are justified.

General:

Provide general conclusion on whether or not all shelf lives and storage conditions defined in the SmPC are justified.

5. CLINICAL PART (SAFETY AND EFFICACY DATA) Split into two

General:

a) Check if the product is new (*new chemical entity*), if YES, evaluate as per ICH guidelines

b) Check if the FPP require therapeutic equivalence data; if not, Check if waiver has been requested, If YES, go to Product Information section.

c) Check if therapeutic equivalence data has been submitted; if not, raise a query requesting for this information.

d) If therapeutic equivalence data has been provided through in vitro studies, confirm acceptability of such studies with requirements for biowaiver. Refer **Annex III** of the ZFDA *Guidelines on Therapeutic Equivalence Requirements. [Biopharmaceutical Classification System (BCS)*].

i) BCS class I – eligible.

ii) BCS class II – eligible if Dose: Solubility ratio (D:S) is 250 ml or less at pH 6.8.

iii) BCS class III – eligible if the FPP is very rapidly dissolving i.e ≥ 85% of API is dissolved in 15 minutes.

iv) BCS class IV – Not eligible

e) If in vivo therapeutic equivalence data has been provided, check and confirm the following: -

i. Did the study get ethical clearance? If not end evaluation by recommending refusal of the product attaching the relevant refusal letter citing lack of safety and efficacy data as the reason for refusal in relation with non-ethical approval.

ii. Were bio-analytical methods validated? If not; end evaluation by recommending refusal of the product attaching the relevant refusal letter citing lack of safety and efficacy data as the reason for refusal in relation with unreliability of bioanalytical results.

f) If requirements under point (d) above are fulfilled, proceed with evaluation as described in the evaluation template.

6. PRODUCT INFORMATION

(*Although this information is under Module 1 of submission guidelines, but it is evaluated last and should be last part of evaluation report*)

6.1 **Container labelling (S4.12)**

Check if labelling meets ZFDA requirements for labelling and give your overall comment. Raise issue(s) if labelling is insufficient.

Comment on each aspect

6.2 **Prescribing Information Leaflet (Summary of Product Characteristics) (S2 and 4.13)**

Check and confirm whether leaflet submitted is comparable to the one approved in the innovator country.

6.3 **Nomenclature (S 2.1-2.4)**

Assess and comment on the name of the medicinal product, dosage form description, ATC and distribution category, INN names and strength of active ingredients.

6.4 **Clinical particulars (S 2.5.1-2.5.9)**

Assess and comment on therapeutic indications posology and method of administration, contraindications, special warnings and precautions for use, interactions, pregnancy and lactation, effects on ability to drive and use machines, undesirable effects and overdose.

6.4.1 Pharmacological properties (S 2.6.1-2.6.3)

Assess and comment on pharmacodynamic and pharmacokinetic properties in different health states.

6.4.2 Pharmaceutical particulars (S 2.7-2.11)

Assess and comment on list of excipients, shelf life, storage instructions pack size and date of revision of text.

6.5 **Patient Information Leaflet (PIL)**

Assess and comment whether PIL meets requirements for language.

7. EVALUATOR'S OVERALL CONCLUSION (in each module)

Give your overall conclusion in relation to quality, safety and efficacy of this product with that registered in the country with stringent medicines regulatory authority. The conclusion must be logical results of the proceeding relationship.

8. AUDITOR'S CONCLUDING REMARKS (in each module)

Give your remarks in relation to evaluator's overall conclusion. Relate the quality, safety and efficacy of this product with that registered in the country with stringent medicines regulatory authority. The conclusion must be logical results of the proceeding relationship.

COMPENDIUM REVISION HISTORY

Revision No:	**Date**	**Author(s)**	**Section(s) revised**	**Description of change**	**Approvals**
00		ZFDA TWG on MER members	All	First approved version to be issued	Doc. No.: ZFDA/MCD/GL/004 Rev 00
01		ZFDA TWG on MER members	1. Part I: Glossary 2. Part I 3.2.S 3. Part I 4. Part III Annexes	1. Stringent Drug Regulatory Authorities redefined 2. API options rearranged in order of preference 3. Inclusion of Quality Information Summary (QIS) 4. Inclusion of Bioequivalence Trial Information Form (BTIF), BCS-Biowaiver application form and Additional strength application form	ZFDA/MCD/COMP/ …..