GUIDELINES ON SUBMISSION OF DOCUMENTATION FOR REGISTRATION[1] OF A PHARMACEUTICAL PRODUCT FOR HUMAN USE

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[1] *In line with the National Drug Policy and Authority Act, Cap. 206 and the National Drug Policy and Authority (Registration) Regulations, 2014, the terms* ***"Registration" and "Holder of a Certificate of Registration"*** *as used in these guidelines are synonymous with the universally accepted term* ***"Marketing Authorization"*** *and* ***"Marketing Authorization Holder"****.*

Safe Drugs Save Lives

Citation

These guidelines shall be cited as the *"Professional Guidelines on Submission of Documentation for Registration of a Pharmaceutical Product for Human Use, Doc. No. PAR/GDL/004, Revision No.:3".*

Adoption and approval of these professional guidelines

In EXERCISE of the powers conferred upon the Drug Authority by Section 5(i) of the National Drug Policy and Authority Act, Cap. 206 of the Laws of Uganda (2000 Edition), the Drug Authority hereby ADOPTS and ISSUES these **Professional Guidelines on Submission of Documentation for Registration of a Pharmaceutical Product for Human Use,** Doc. No. PAR/GDL/004, Revision No.:3, made this 15th day of February 2023, that take effect on 20th February 2023.

Signature

Dr. Medard Bitekyerezo
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INTRODUCTION

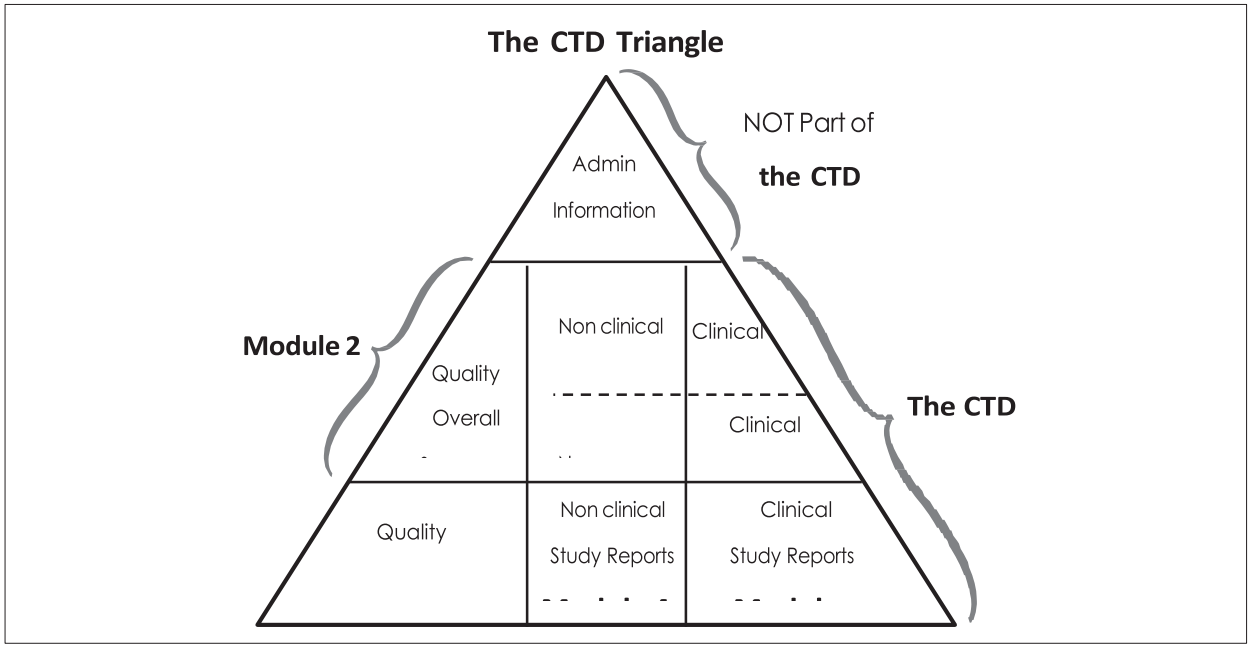
National Drug Authority (NDA) was established in 1993 by the National Drug Policy and Authority Statute which in 2000 became the National Drug Policy and Authority (NDP/A) Act, Cap. 206 of the Laws of Uganda (2000 Edition). The Act established a National Drug Policy and National Drug Authority to ensure the availability, at all times, of essential, efficacious and cost-effective drugs to the entire population of Uganda, as a means of providing satisfactory healthcare and safeguarding the appropriate use of drugs.

"The National Drug Policy and Authority Act, Section 35 mandates NDA to scientifically examine any drug for purposes of ascertaining efficacy, safety and quality of a drug before registration for use in Uganda.

The Common Technical Document (CTD) format which involves the assembling of all quality, safety and efficacy information in a common format called CTD has revolutionized the regulatory review processes and has led to harmonized electronic submission that in turn has enabled implementation of good review practices. These guidelines, which require use of the Common Technical Document (CTD) format shall be followed by all applicants when preparing applications for Marketing Authorization of Pharmaceutical Products for Human use intended for submission to NDA.

The CTD is organised into five modules (see the CTD triangle in Figure 1 below). Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions. Applicants should not modify the overall organisation of the CTD.

Figure 1:



Any additional data, if not contained in the bulk of the documentation, should be included as addenda to the relevant part, together with additional expert comment that may be

provided as a supplement to, or incorporated into, the relevant summary, overall summary or overview.

1.1. Objective of these guidelines

These guidelines are intended to provide guidance to applicants to prepare product dossiers in CTD format for submission to NDA.

1.2. Policy

These guidelines are developed in accordance with the National Drug Policy and Authority Act Cap 206;

Section 35(1)(a): *"the drug authority may scientifically examine any drug for the purposes of ascertaining efficacy, safety and quality of that drug"*

Section 35(3) *"if, on application made in the prescribed manner and on payment of the prescribed fee, the Authority is satisfied that the drug or preparation in respect of which the application is made has not been registered; and that the use of the drug or preparation is likely to prove beneficial, the Authority shall register the name and description of that drug or preparation".*

1.3. Scope

These guidelines apply to product dossiers for chemical pharmaceutical products containing existing APIs of synthetic or and new APIs.

These guidelines do not apply to vaccines, biosimilars, biotherapeutics and herbal preparations.

GLOSSARY OF TERMS

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) 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.

Active pharmaceutical ingredient (API): An active pharmaceutical 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.

Active pharmaceutical ingredient: A substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a pharmacologically active compound (ingredient).

Agent (Local Technical Representative (LTR)): Every applicant who is not resident in Uganda shall appoint a person in Uganda and authorized by NDA to deal in medicinal products to be an AGENT (Local Technical Representative (LTR). The appointment shall be notified to the Authority by submitting a letter of appointment supported by original copy of power of attorney. Dully notarised in country of origin, and registered with registrar of Companies in Uganda.

Applicant: means any person who submits an application for registration to the Authority and may be a patent holder; licensed person; the manufacturer; or an agent authorized by the manufacturer or patent holder.

The applicant shall therefore be responsible for signing the registration application form. In the event that the applicant wants another person to register the medicinal product on his behalf, then Powers of Attorney, duly notarised in the country of origin, and registered with the Registrar of Companies in Uganda shall be provided. After the product is registered, the applicant shall be the Holder of a Certificate of Registration.

Authorized person: A person responsible for the release of batches of finished product for sale or distribution. The batch documentation of a batch of a finished product must be signed by an authorized person from the production department and the batch test results by an authorized person from the quality control department for batch release.

Authorized pharmacopoeia (or compendium): The current edition of any of the International Pharmacopoeia (the British Pharmacopoeia, the European Pharmacopoeia and United States Pharmacopeia.

Batch (or lot): A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it could be expected to be homogeneous. In the case of continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch.

Batch number (or lot number): A distinctive combination of numbers and/or letters which specifically identifies a batch on the labels, the batch records, the certificates of analysis, etc.

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

Bulk product: Any product that has completed all processing stages up to, but not including, final packaging.

Calibration: The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording, and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

Certification: The final review and formal approval of a validation or revalidation, followed by approval of a process for routine use.

Challenge tests/worst case: A condition or set of conditions encompassing upper and lower processing limits and circumstances, within standard operating procedures, that pose the greatest chance of process or product failure when compared with ideal conditions.

Clean area: An area with defined environmental control of particulate and microbial contamination; constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area.

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.

Critical process: A process that may cause variation in the quality of the pharmaceutical product.

Cross-contamination: Contamination of a starting material, intermediate product, or finished product with another starting material or product during production.

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.

Generic product: 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.

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

In-process control: Checks performed during production in order to monitor and if necessary to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

Installation qualification: The performance of tests to ensure that the installations (such as machines, measuring devices, utilities, manufacturing areas) used in a manufacturing process are appropriately selected and correctly installed and operate in accordance with established specifications.

Intermediate product: Partly processed material that must undergo further manufacturing steps before it becomes a bulk product.

Large-volume parenterals: Sterile solutions intended for parenteral application with a volume of 100 ml or more in one container of the finished dosage form.

Manufacture: All operations of purchase of materials and products, production, packaging, quality control, release, storage, shipment of finished products, and the related controls.

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.

Manufacturing process: The transformation of starting materials into finished products (drug substances or pharmaceutical dosage forms) through a single operation or a

sequence of operations involving installations, personnel, documentation and environment.

Marketing authorization (product licence, registration certificate): A legal document issued by the competent drug regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labeling and shelf-life.

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

Master record: A document or set of documents that serve as a basis for the batch documentation (blank batch record).

Finished product or finished pharmaceutical product (FPP): A product that has undergone all stages of production, including packaging in its final container and labeling.

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

Operational qualification: Documented verification that the system or subsystem performs as intended over all anticipated operating ranges.

Packaging material: Any material, including printed material, employed in the packaging of a pharmaceutical product, excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

Packaging: All operations, including filling and labeling, that a bulk product has to undergo in order to become a finished product. Sterile filling would not normally be regarded as part of packaging, the bulk product being the filled, but not the finally packaged, primary container.

Pharmaceutical product: Any medicine intended for human use or veterinary product administered to food-producing animals, presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in both the exporting state and the importing state.

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

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

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

Production: All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing and packaging, to completion of the finished product.

Qualification of equipment: The act of planning, carrying out and recording the results of tests on equipment to demonstrate that it will perform as intended. Measuring instruments and systems must be calibrated.

Reconciliation: A comparison, making due allowance for normal variation, between the amount of product or materials theoretically produced or used and the amount actually produced or used.

Recovery (or blending): The introduction of all or part of previous batches (or of redistilled solvents and similar products) of the required quality into another batch at a defined stage of manufacture.

Reprocessing: The reworking of all or part of a batch of product of an unacceptable quality from a defined stage of production so that its quality may be rendered acceptable by one or more additional operations.

Revalidation: Repeated validation of an approved process (or a part thereof) to ensure continued compliance with established requirements.

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

Standard operating procedure (SOP): An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material but of a more general nature (e.g., equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

Starting material: Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

Stringent regulatory authority (SRA): A regulatory authority which is a member of the International Conference on Harmonisation (ICH) (as specified on www.ich.org); or an ICH observer, being the European Free Trade Association (EFTA), as represented by Swiss Medic, and Health Canada (as may be updated from time to time); or a regulatory authority associated with an ICH member through a legally- binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time).

System: A regulated pattern of interacting activities and techniques that are united to form an organized whole.

Validation protocol (or plan): A document describing the activities to be performed in a validation, including the acceptance criteria for the approval of a manufacturing process or a part thereof for routine use.

Validation report: A document in which the records, results and evaluation of a completed validation program are assembled. It may also contain proposals for the improvement of processes and/or equipment.

Validation: The documented act of proving that any procedure, process, equipment, material, activity, or system actually leads to the expected results.

PROCEDURE FOR SUBMISSION OF AN APPLICATION IN CTD FORMAT

a) The application should be typed in English. Any documents which are in any language other than English must be accompanied by a certified or notarized English translation.

b) The application must contain a complete index to the various appendices.

c) The summaries (Quality Information Summary, Quality Overall Summary, Bioequivalence Trial Information, Biopharmaceutical Classification System (BCS) and additional strength Biowaiver Application Forms) should be formatted as word document, and the body data in PDF format with bookmarks and optical character recognition (OCR) readable.

d) All pages of the application should be numbered in the style: page x of y.

e) Fees for Marketing Authorization applications should be paid before submitting the application. Refer to the NDA website for the fees regulation.

f) Payment of fees can be made to: National Drug Authority on UGX account number: 9030005759829, or US Dollars account number: 9030008068851; in Stanbic Bank Uganda, Kampala.

g) The application should be submitted in CD-ROM addressed to: The Secretary to the Authority, National Drug Authority.

h) All submissions such as QIS/QOS P-D, PIL, BTIF and the Summary of the Product Characteristics should be in the exact format/template prescribed in the appendices of this guideline.

i) A separate application is required for each product. The following products will be regarded as either being the same product or separate product applications.

TYPE OF APPLICATIONS			Application	
			Same	Separate
1.	**Each individual dosage form of a particular medicine**			X
2.	**Variations of the active pharmaceutical ingredient (API) of a product**			X
3.	**Tablets/Capsules/Suppositories/Lozenges**			
	a)	Different pack-sizes of exactly the same strength and formulation.	X	
	b)	Different strengths and formulations.		X
	c)	Uncoated and coated tablets of the same strength and formulation.		X
4.	**Syrups/Liquids/Solutions (excluding parenterals)/Creams/ Ointments**			
	a)	Different container sizes of the same strength and formulation.	X	

TYPE OF APPLICATIONS			Application	
			Same	Separate
	b)	The same container size of different strengths and formulations.		X
5.	**Ampoules and Vials and Large Volume Parenterals**			
	a)	Ampoules or single dose vials containing identical solutions of the same strength but of different volumes (i.e. resulting in different total doses).		X
	b)	Ampoules containing solutions of different strengths.		X
	c)	Ampoules and single dose vials containing e.g. dry powder, crystals of different mass.		X
	d)	Ampoules and single dose vials containing the same respective masses of e.g. dry powder, crystals.	X	
	e)	Ampoules, single dose vials, as well as pre-filled disposable syringes and cartridges containing identical solutions of the same strength and same volume of liquid.	X	
	f)	Dental cartridges containing different volumes of fluids of the same strength (provided the dose remains constant).	X	
	g)	Ampoules containing "water for injection", but of different volumes.	X	
	h)	Special ampoules of dry powder and "water for injections" contained in the same unit, but intended for mixing at the time of injection if water for injections is fully described in dossier.	X	
	i)	Ampoules containing identical solutions of different volumes used only as diluent in the reconstitution of a preparation for parenteral use.	X	
	j)	Multidose vials containing different volumes of the same strength and formulation with the same dosage schedule.	X	
	k)	Multidose vials and a single dose ampoule or vial of the same formulation if the single-dose ampoule or vial corresponds to the dose indicated for the multidose vial.	X	
	l)	Multidose vials containing dry powder of different mass of the same formulation, and the same concentration when reconstituted.	X	
	m)	An ampoule of diluent packed together with any preparation including biological medicines if diluent is fully described in dossier.	X	
	n)	Infusion solutions of the different volumes and of the same formulation which are packed in containers of exactly the same type of material depending on the relevant information submitted.	X	
	o)	Infusion solutions of the same formulation and of the same or different volume which are packed in containers made of different types of materials.	X	
	P)	A preparation, packed in plastic containers, intended to be marketed in glass containers containing the same volume and the same formulation.	X	

TYPE OF APPLICATIONS			Application	
			Same	Separate
	q)	Products with the same strength and formulation but with different colours and/or flavours.		X
	r)	Applications containing the same API(s) applying for additional indications which render the product in a different scheduling status, or different pharmacological classification, or have any other restrictions imposed other than the original application.		X
	s)	Removal of antimicrobial preservative from single dose presentation of registered vaccine that included a preservative in the original approved formulation		X
6.	**Same formulation with different proprietary names whether of the same or different applicants**			X

ADDITIONAL INFORMATION

a) Where the information or documents submitted in respect of an application for registration are not sufficient for the Authority to determine whether the product to be registered meets the quality, safety and efficacy requirements determined by the Authority, the Authority may request the applicant to submit additional information necessary for the registration. A letter to this effect will be sent to the applicant.

b) A period of 6 months from the date of issue of the letter to the applicant is the time within which the applicant should provide the complete and correct information as requested for in the letter.

c) Only consequential changes will be accepted during assessment. Major changes or additions to the submitted application before registration will be required to re-submit the entire application with the new information.

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 organised 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.

1.1 Comprehensive table of contents for all modules

1.2 Cover letter

Applicants should include a cover letter (refer to Appendix 1 - *Format for CTD 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 proposed Holder of a Certificate of Registration.

1.3 Comprehensive table of contents

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.

1.4 Quality Information Summary (QIS)

The Quality Information Summary (QIS) template (refer to Appendix 2 - *Template for Quality Information Summary*) should be completed to provide a condensed summary of the key quality information for the PD and constitutes part of the submission package. The QIS provides an accurate record of technical data in the PD at the time of prequalification. The QIS is a condensed version of the QOS-PD in section 2.3 and represents the final agreed-upon key information on the API and FPP from the PD assessment (including, but not limited to, identification of the manufacturer(s), site addresses, API/FPP specifications, stability conclusions and relevant commitments).

1.5 Product Information

Provide copies of all package inserts, labels and any information intended for distribution with the product to the patient. All medicinal preparations with potential for long-term use and self-administered injections must contain a patient information leaflet.

1.5.1 Prescribing information (Summary of products characteristics)

Refer to Appendix 3 - *Guidelines on Format and Content of Summary of Product Characteristics for Pharmaceutical Products*.

1.5.2 Container labelling

Refer to Appendix 4 - *Guidelines on Format and Content of Labels for Pharmaceutical Products*

1.5.3 Patient information leaflet (PIL)

Refer to Appendix 5 - *Guidelines on Format and Content of Patient Information Leaflets for Pharmaceutical Products*

1.5.4 Mock-ups and specimens

If the product applicant has a specimen or mock-up of the sales presentation of the medicine available at the time of initial application, it should be included in Module1.4.4. Acceptance of Mock samples and artwork of the product for registration shall be determined by the Authority

1.6 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:

a) The Quality Overall Summary, Non-clinical Overview / Summary and
b) Clinical Overview / Summary in Module 2,
c) A declaration signed by the experts in Module 1.6.
d) 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 in Appendix 6 - *Format for Declaration by Expert.*

1.7 APIMFs and certificates of suitability to the monographs of the European Pharmacopoeia

An application to register a new pharmaceutical product (or vary an existing product) may make reference to an Active Pharmaceutical Master File (APIMF) or certificate of suitability to the monographs of the European Pharmacopoeia (CEP).

Where reference is made to an APIMF, the FPP applicant must have written permission to access the APIMF from the APIMF holder and must provide the APIMF file number to NDA.

Where reference is made to a CEP, the finished product applicant must have written permission from the API manufacturer to access the CEP and must provide a copy of the CEP, and any appendices, to NDA.

Complete copies of the CEP (including any annexes) should be provided in Module 1.7

Procedures relating to APIMFs and CEPs are outlined in more detail in Module 3.

The applicant should provide the Letter of Access to APIMF or Letter of Access to CEP, as appropriate from API manufacturer (refer to Appendix 7 - Formats for Letters of Access to APIMF and CEP). These letters 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 NDA directly by the API manufacturer when required.

1.8 Good Manufacturing Practice

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 GMP.

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

1.9 Regulatory status within EAC and in countries with SRAs

1.9.1 List of countries in EAC and countries with SRAs 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 EAC and countries with SRAs 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.

1.9.2 Evaluation reports from EAC-NMRA

Provide copies of evaluation reports from EAC-NMRAs in Module 1.9.2 if available.

1.9.3 Evaluation reports from SRAs

At least one independent evaluation report from an SRA, where the product is already approved at the time of application, should be provided in Module 1.9.3.

1.9.4 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 FPP by WHO should be submitted.

1.10 Paediatric development program

Please state whether there is a paediatric development program for this medicine and if so, identify the relevant sections of the dossier.

1.11 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.

1.12 Requirement for submission of a risk mitigation plan

The summary of the pharmacovigilance system should be provided as part of the application for registration and include the following elements:

a) proof that the applicant or their agent (LTR) has at their disposal a Qualified Person for Pharmacovigilance (QPPV) in Uganda. The contact details of the QPPV should be specified;

b) a statement signed by the applicant or their agent (LTR) to the effect that the applicant has the necessary means to fulfill the tasks and responsibilities listed in the Pharmacovigilance regulations and guidelines on Submission of Documentation for Registration of a Pharmaceutical Product for Human Use in Uganda.

1.13 Submission of risk management (RMP)

Applicants are required to submit a risk-management plan (RMP) for products as shall be determined by NDA. Refer to the NDA website for the current list of products that require mandatory RMP when applying for registration.

In addition, for registered pharmaceutical products NDA can request an RMP whenever there is a concern about a risk affecting the benefit-risk balance of a drug.

RMPs are continually modified and updated throughout the lifetime of the drug as new information becomes available. Submission or RMPs shall therefore be necessary under the following circumstances:

a) Products for which RMPs were submitted at time of registration, the Holder of a Certificate of Registration shall be required to submit periodic safety update report and any other reports that may be relevant to determine the safety, efficacy and quality of a drug;

b) At the request of the Authority when there is a concern about risk affecting the risk-benefit balance.

MODULE 2: OVERVIEW AND SUMMARIES

2.1 Table of contents of Module 2

A table of contents for the filed product dossier should be provided.

2.2 CTD introduction

This section should be a 2-3-page summary of the entire application.

2.3 Quality overall summary - product dossiers (QOS-PD)

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 CTD.

The QOS should include sufficient information from each section to provide the quality assessor with an overview of Module 3. The QOS should also emphasize critical key parameters of the product and provide, for instance, justification in cases where guidelines were not followed. The QOS should include a discussion of key issues that integrates information from sections in the Quality Module and supporting information from other Modules (e.g. qualification of impurities via toxicological studies), including cross-referencing to volume and page number in other Modules.

The quality overall summary - product dossiers (QOS-PD) template (refer to Appendix 8 - *Template for Quality Overall Summary - Product Dossier)* should be completed for generic pharmaceutical products containing APIs of synthetic or semisynthetic origin and their corresponding FPPs.

All sections and fields in the QOS-PD template that would be applicable should be completed. It is understood that certain sections and fields may not apply and should be indicated as such by reporting “not applicable” in the appropriate area with an accompanying explanatory note.

The use of tables to summarize the information is encouraged, where possible. The tables included in the template may need to be expanded or duplicated (e.g. for multiple strengths), as necessary. These tables are included as illustrative examples of how to summarize information. Other approaches to summarize information can be used if they fulfil the same purpose.

2.4 Nonclinical overview for new chemical entities

The Nonclinical 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. This section is not applicable for generic drugs.

2.5 Clinical Overview

2.5.1 Product Development Rationale

The discussion of the rationale for the development of the FPP should:

a) Identify the pharmacological class of the FPP.

b) Describe the particular clinical/pathophysiological condition that the FPP is intended to treat, prevent, or diagnose (the targeted indication).

c) Briefly summarise the scientific background that supported the investigation of the FPP for the indication(s) that was (were) studied.

d) Briefly describe the clinical development programme of the FPP, including ongoing and planned clinical studies and the basis for the decision to submit the application at this point in the programme. Briefly describe plans for the use of foreign clinical data (ICH E5).

e) Note and explain concordance or lack of concordance with current standard research approaches regarding the design, conduct and analysis of the studies. Pertinent published literature should be referenced. Regulatory guidance and advice (at least from the region(s) where the Clinical Overview is being submitted) should be identified, with discussion of how that advice was implemented. Formal advice documents (e.g., official meeting minutes, official guidance, letters from regulatory authorities) should be referenced, with copies included in the references section of Module 5.

2.5.2 Overview of Bio-pharmaceutics

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

2.5.3 Overview of Clinical Pharmacology

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

a) Pharmacokinetics, e.g., comparative PK in healthy subjects, patients, and special populations; PK related to intrinsic factors (e.g., age, sex, race, renal and hepatic impairment) and to extrinsic factors (e.g., smoking, concomitant drugs, diet); rate and extent of absorption; distribution, including binding with plasma proteins; specific metabolic pathways, including effects of possible genetic

polymorphism and the formation of active and inactive metabolites; excretion; time-dependent changes in pharmacokinetics; stereochemistry issues; clinically relevant PK interactions with other FPPs or other substances.

b) Pharmacodynamics, e.g., information on mechanism of action, such as receptor binding; onset and/or offset of action; relationship of favorable and unfavorable pharmacodynamic effects to dose or plasma concentration (i.e., PK/PD relationships); PD support for the proposed dose and dosing interval; clinically relevant PD interactions with other FPPs or substances; and possible genetic differences in response.

c) Interpretation of the results and implications of immunogenicity studies, clinical microbiology studies, or other drug class specific PD studies summarised in section 2.7.2.4 of the Clinical Summary.

2.5.4 Overview of Efficacy

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

Prematurely terminated studies should be noted and their impact considered. The following issues should generally be considered:

a) Relevant features of the patient populations, including demographic features, disease stage, any other potentially important covariates, any important patient populations excluded from critical studies, and participation of children and elderly (ICH E11 and E7). Differences between the studied population(s) and the population that would be expected to receive the FPP after marketing should be discussed.

b) Implications of the study design(s), including selection of patients, duration of studies and choice of endpoints and control group(s). Particular attention should be given to endpoints for which there is limited experience. Use of surrogate endpoints should be justified. Validation of any scales used should be discussed.

c) For non-inferiority trials used to demonstrate efficacy, the evidence supporting a determination that the trial had assay sensitivity and justifying the choice of non-inferiority margin (ICH E10).

d) Statistical methods and any issues that could affect the interpretation of the study results (e.g., important modifications to the study design, including endpoint assessments and planned analyses, as they were specified in the original protocol;

e) Support for any unplanned analyses; procedures for handling missing data; and corrections for multiple endpoints).

f) Similarities and differences in results among studies, or in different patient sub-groups within studies, and their effect upon the interpretation of the efficacy data.

g) Observed relationships between efficacy, dose, and dosage regimen for each indication, in both the overall population and in the different patient subgroups (ICH E4).

h) Support for the applicability to the new region of data generated in another region, where appropriate (ICH E5).

i) For products intended for long-term use, efficacy findings pertinent to the maintenance of long-term efficacy and the establishment of long-term dosage. Development of tolerance should be considered.

j) Data suggesting that treatment results can be improved through plasma concentration monitoring, if any, and documentation for an optimal plasma concentration range.

k) The clinical relevance of the magnitude of the observed effects.

l) If surrogate endpoints are relied upon, the nature and magnitude of expected clinical benefit and the basis for these expectations.

m) Efficacy in special populations. If efficacy is claimed with inadequate clinical data in the population, support should be provided for extrapolating efficacy from effects in the general population.

2.5.5 Overview of Safety

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

a) Adverse effects characteristic of the pharmacological class. Approaches taken to monitor for similar effects should be described.

b) Special approaches to monitoring for particular adverse events (e.g., ophthalmic, QT interval prolongation).

c) Relevant animal toxicology and product quality information. Findings that affect or could affect the evaluation of safety in clinical use should be considered.

d) The nature of the patient population and the extent of exposure, both for test drug and control treatments.

e) Limitations of the safety database, e.g., related to inclusion/exclusion criteria and study subject demographics, should be considered, and the implications of such limitations with respect to predicting the safety of the product in the marketplace should be explicitly discussed.

f) Common and non-serious adverse events, with reference to the tabular presentations of events with the test drug and with control agents in the Clinical Summary. The discussion should be brief, focusing on events of relatively high

frequency, those with an incidence higher than placebo, and those that are known to occur in active controls or other members of the therapeutic class. Events that are substantially more or less common or problematic (considering the duration and degree of the observed events) with the test drug than with active controls are of particular interest.

g) Serious adverse events (relevant tabulations should be cross-referenced from the Clinical Summary). This section should discuss the absolute number and frequency of serious adverse events, including deaths, and other significant adverse events (e.g., events leading to discontinuation or dose modification), and should discuss the results obtained for test drug versus control treatments. Any conclusions regarding causal relationship (or lack of this) to the product should be provided. Laboratory findings reflecting actual or possible serious medical effects should be considered.

h) Similarities and differences in results among studies, and their effect upon the interpretation of the safety data.

i) Any differences in rates of adverse events in population subgroups, such as those defined by demographic factors, weight, concomitant illness, concomitant therapy, or polymorphic metabolism.

j) Relation of adverse events to dose, dose regimen, and treatment duration.

k) Long-term safety (E1a).

l) Methods to prevent, mitigate, or manage adverse events.

m) Reactions due to overdose; the potential for dependence, rebound phenomena and abuse, or lack of data on these issues.

n) World-wide marketing experience. The following should be briefly discussed:

   i. the extent of the world- wide experience,

   ii. any new or different safety issues identified.

   iii. any regulatory actions related to safety.

o) Support for the applicability to the new region of data generated in another region, where appropriate (ICH E5).

2.5.6 Benefits and Risks Conclusions

The purpose of this section is to integrate all of the conclusions reached in the previous sections about the biopharmaceutics, clinical pharmacology, efficacy and safety of the FPP and to provide an overall appraisal of the benefits and risks of its use in clinical practice. Also, implications of any deviations from regulatory advice or guidelines and any important limitations of the available data should be discussed here. This assessment should address critical aspects of the proposed Prescribing Information. This section should also consider the risks and benefits of the FPP as they compare to available alternative treatments or to no treatment in illnesses where no treatment may

be a medically acceptable option; and should clarify the expected place of the FPP in the armamentarium of treatments for the proposed indication.

If there are risks to individuals other than those who will receive the drug, these risks should be discussed (e.g., risks of emergence of drug-resistant bacterial strains with widespread use of an antibiotic for minor illnesses). The analyses provided in previous sections should not be reiterated here. This section often can be quite abbreviated when no special concerns have arisen and the drug is a member of a familiar pharmacological class.

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

a) The efficacy of the FPP for each proposed indication.

b) Significant safety findings and any measures that may enhance safety.

c) Dose-response and dose-toxicity relationships; optimal dose ranges and dosage regimens.

d) Efficacy and safety in sub-populations, e.g., those defined by age, sex, ethnicity, organ function, disease severity, and genetic polymorphisms.

e) Data in children in different age groups, if applicable, and any plans for a development programme in children.

f) Any risks to the patient of known and potential interactions, including food- drug and drug-drug interactions, and recommendations for product use.

g) Any potential effect of the FPP that might affect ability to drive or operate heavy machinery.

h) Examples of issues and concerns that could warrant a more detailed discussion of benefits and risks might include: The drug is for treatment of a non-fatal disease but has known or potential serious toxicity, such as a strong signal of carcinogenicity, teratogenicity, pro-arrhythmic potential (effect on QT interval), or suggestion of hepatotoxicity.

i) The proposed use is based on a surrogate endpoint and there is a well-documented important toxicity.

j) Safe and/or effective use of the drug requires potentially difficult selection or management approaches that require special physician expertise or patient training.

2.5.7 Literature References

A list of references used, stated in accordance with the current edition of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, International Committee of Medical Journal Editors (ICMJE)*or the system used in — Chemical Abstracts, should be provided. Copies of all references cited in the Clinical Overview should be provided in Section 5.1.4 of Module 5.

2.6 Non-clinical Written and Tabulated Summaries

This section is applicable to generic products.

The primary purpose of the Nonclinical Written and Tabulated Summaries should be to provide a comprehensive factual synopsis of the nonclinical data. The interpretation of the data, the clinical relevance of the findings, cross-linking with the quality aspects of the pharmaceutical, and the implications of the nonclinical findings for the safe use of the pharmaceutical (i.e., as applicable to labeling) should be addressed in the Overview.

2.6.1 Nonclinical Written Summaries

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

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

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

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

Order of Presentation of Information within Sections

When available, in vitro studies should precede in vivo studies.

Where multiple studies of the same type need to be summarised within the Pharmacokinetics and Toxicology sections, studies should be ordered by species, by route, and then by duration (shortest duration first).

Species should be ordered as follows:

a) Mouse
b) Rat
c) Hamster
d) Other rodent
e) Rabbit
f) Dog

g) Non-human primate
h) Other non-rodent mammal
i) Non-mammals

Routes of administration should be ordered as follows:

a) The intended route for human use
b) Oral
c) Intravenous
d) Intramuscular
e) Intraperitoneal

Subcutaneous

a) Inhalation
b) Topical
c) Other

Use of Tables and Figures

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

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

Throughout the text, reference citations to the Tabulated Summaries should be included.

Length of Nonclinical Written Summaries

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

Sequence of Written Summaries and Tabulated Summaries

The following order is recommended:

a) Introduction
b) Written Summary of Pharmacology
c) Tabulated Summary of Pharmacology
d) Written Summary of Pharmacokinetics
e) Tabulated Summary of Pharmacokinetcs
f) Written Summary of Toxicology

g) Tabulated Summary of Toxicology

Content of Nonclinical Written and Tabulated Summaries

2.6.2 Introduction

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

Brief information concerning the pharmaceutical structure (preferably, a structure diagram should be provided) and pharmacological properties.

Information concerning the pharmaceutical product's proposed clinical indication, dose, and duration of use.

2.6.3 Pharmacology Written Summary

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

a) Brief Summary
b) Primary Pharmacodynamics
c) Secondary Pharmacodynamics
d) Safety Pharmacology
e) Pharmacodynamic Drug Interactions
f) Discussion and Conclusions
g) Tables and Figures (either here or included in text)

2.6.3.1 Brief Summary

The principal findings from the pharmacology studies should be briefly summarized in approximately 2 to 3 pages. This section should begin with a brief description of the content of the pharmacologic data package, pointing out any notable aspects such as the inclusion/exclusion of particular data (e.g., lack of an animal model).

2.6.3.2 Primary Pharmacodynamics

Studies on primary pharmacodynamics* should be summarised and evaluated. Where possible, it would be helpful to relate the pharmacology of the drug to available data (in terms of selectivity, safety, potency, etc.) on other drugs in the class.

2.6.3.3 Secondary Pharmacodynamics

Studies on secondary pharmacodynamics* should be summarised by organ system, where appropriate, and* evaluated in this section.

*Reference: See ICH Guideline S7, Safety Pharmacology Studies for Human Pharmaceuticals, Note 2. p. 8, for definitions.

2.6.3.4 Safety Pharmacology

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

2.6.3.5 Pharmacodynamic Drug Interactions

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

2.6.3.6 Discussion and Conclusions

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

2.6.3.7 Tables and Figures

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

2.6.4 Pharmacology Tabulated Summary

2.6.5 Pharmacokinetics Written Summary

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

a) Brief Summary

b) Methods of Analysis

c) Absorption

d) Distribution

e) Metabolism

f) Excretion

g) Pharmacokinetic Drug Interactions

h) Other Pharmacokinetic Studies

i) Discussion and Conclusions

j) Tables and Figures (either here or included in text)

2.6.5.1 Brief Summary

The principal findings from the pharmacokinetics studies should be briefly summarized in approximately 2 to 3 pages. This section should begin with a description of the scope of the pharmacokinetic evaluation, emphasising, for example, whether the species and strains examined were those used in the pharmacology and toxicology evaluations, and whether the formulations used were similar or identical.

2.6.5.2 Methods of Analysis

This section should contain a brief summary of the methods of analysis for biological samples, including the detection and quantification limits of an analytical procedure. If possible, validation data for the analytical method and stability of biological samples should be discussed in this section. The potential impact of different methods of analysis on the interpretation of the results should be discussed in the following relevant sections.

2.6.5.3 Absorption

The following data should be summarised in this section:

a) Absorption (extent and rate of absorption, in vivo and in situ studies)

b) Kinetic parameters, bioequivalence and/or bioavailability (serum/plasma/ blood PK studies)

2.6.5.4 Distribution

The following data should be summarised in this section:

a) Tissue distribution studies

b) Protein binding and distribution in blood cells

c) Placental transfer studies

2.6.5.5 Metabolism (interspecies comparison)

The following data should be summarised in this section:

a) Chemical structures and quantities of metabolites

b) in biological samples

c) Possible metabolic pathways

d) Pre-systemic metabolism (Gl/hepatic first-pass effects)

e) In vitro metabolism including P450 studies

f) Enzyme induction and inhibition

2.6.5.6 Excretion

The following data should be summarised in this section:

a) Routes and extent of excretion

b) Excretion in milk

2.6.5.7 Pharmacokinetic Drug Interactions

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

2.6.5.8 Other Pharmacokinetic Studies

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

2.6.5.9 Discussion and Conclusions

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

2.6.5.10 Tables and Figures

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

2.6.6 Pharmacokinetics Tabulated Summary

2.6.7 Toxicology Written Summary

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

a) Brief Summary
b) Single-Dose Toxicity
c) Repeat-Dose Toxicity
d) Genotoxicity
e) Carcinogenicity
f) Reproductive and Developmental Toxicity
g) Studies in Juvenile Animals
h) Local Tolerance
i) Other Toxicity Studies
j) Discussion and Conclusions
k) Tables and Figures (either here or included in text)

2.6.7.1 Brief Summary

The principal findings from the toxicology studies should be briefly summarized in a few pages (generally not more than 6). In this section, the extent of the toxicology evaluation can be indicated by the use of a table listing the principal toxicology studies (results should not be presented in this table), for example:

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

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

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

a) Fertility and early embryonic development

b) Embryo-fetal development

c) Prenatal and postnatal development, including maternal function

d) Studies in which the offspring (juvenile animals) are dosed and/or further evaluated, if such studies have been conducted.

If modified study designs are used, the sub-headings should be modified accordingly.

2.6.7.2 Single-Dose Toxicity

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

2.6.7.3 Repeat-Dose Toxicity (including supportive toxicokinetics evaluation)

Studies should be summarised in order by species, by route, and by duration, giving brief details of the methodology and highlighting important findings (e.g., nature and severity of target organ toxicity, dose (exposure)/ response relationships, no observed adverse effect levels, etc.). Non-pivotal studies can be summarized in less detail (pivotal studies are the definitive GLP studies specified by ICH Guideline M3).

2.6.7.4 Genotoxicity

Studies should be briefly summarised in the following order:

a) in vitro non-mammalian cell system

b) in vitro mammalian cell system

c) in vivo mammalian system (including supportive toxicokinetics evaluation)

d) other systems

2.6.7.5 Carcinogenicity (including supportive toxicokinetics evaluations)

A brief rationale should explain why the studies were chosen and the basis for high- dose selection. Individual studies should be summarised in the following order:

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

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

c) Other studies

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

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

Fertility and early embryonic development

a) Embryo-fetal development

b) Prenatal and postnatal development, including maternal function

c) Studies in which the offspring (juvenile animals) are dosed and/or further evaluated, if such studies have been conducted.

If modified study designs are used, the sub-headings should be modified accordingly.

2.6.7.7 Local Tolerance

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

2.6.7.8 Other Toxicity Studies (if available)

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

a) Antigenicity

b) Immunotoxicity

c) Mechanistic studies (if not reported elsewhere)

d) Dependence

e) Studies on metabolites

f) Studies on impurities

g) Other studies

2.6.7.9 Discussion and Conclusions

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

2.6.7.10 Tables and Figures

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

2.6.8 Toxicology Tabulated Summary Nonclinical Tabulated Summaries

It is recommended that summary tables for the nonclinical information in the Common Technical Document be provided in the format outlined in this Guideline. Applicants can modify the format if needed to provide the best possible presentation of the information and to facilitate the understanding and evaluation of the results.

This Guideline is not intended to indicate what studies are requested, but solely to advise how to tabulate study results if a study is performed. Applicants might need to add some items to or delete some items from the cited format where appropriate. One tabular format can contain results from several studies. Alternatively, it may be appropriate to cite the data resulting from one study in several tabular formats.

The recommended formats for the tables in the Nonclinical Tabulated Summaries are follows ICH guidelines. However, it is the responsibility of the applicant to decide on the best possible presentation of the data for each product. Authors should keep in mind that, in some regions, a review of the Tabulated Summaries (in conjunction with the Written Summaries) represents the primary review of the nonclinical information. Presentation of the data in the formats provided as templates and examples should ensure that a sufficient level of detail is available to the reviewer and should provide concise overviews of related information.

When a juvenile-animal study has been conducted, it should be tabulated using the template appropriate for the type of study.

The order of presentation given for the Nonclinical Written Summaries should be followed for the preparation of the tables for the Nonclinical Tabulated Summaries.

2.7 Clinical summary

The Clinical Summary is intended to provide a detailed, factual summarisation of all of the clinical information in the application. This includes information provided in ICH E3 clinical study reports; information obtained from any metaanalyses 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. The comparisons and analyses of results across studies provided in this document should focus on factual observations. In contrast, the Clinical Overview document should provide critical analysis of the clinical study program and its results, including discussion and interpretation of the clinical findings and discussion of the place of the test drug in the armamentarium.

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

2.7.1 Summary of Biopharmaceutics Studies and Associated Analytical Methods

For generic products, Overview, summaries and conclusion should be filled in Bioequivalence Trial Information Summary (BITF) (refer to Appendix 9 - *Presentation of Bioequivalence Trial Information*).

2.7.1.1 Background and Overview

This section should provide the reviewer with an overall view of the formulation development process, the in vitro and in vivo dosage form performance, and the general approach and rationale used in developing the bioavailability (BA), comparative BA, bioequivalence (BE), and in vitro dissolution profile database.

Reference should be made to any guidelines or literature used in planning and conducting the studies. This section should also provide the reviewer with an overview of the analytical methods used, with emphasis on the performance characteristics of assay validation (e.g., linearity range, sensitivity, specificity) and quality control (e.g., accuracy and precision). This section should not include detailed information about individual studies.

2.7.1.2 Summary of Results of Individual Studies

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

2.7.1.3 Comparison and Analyses of Results Across Studies

This section should provide a factual summary of all in vitro dissolution, BA, and comparative BA studies carried out with the drug substance or drug product, with particular attention to differences in results across studies. This overview should typically summarise the findings in text and tables and should consider the following:

a) Evidence of the effects of formulation and manufacturing changes on in vitro dissolution and BA and conclusions regarding BE. When manufacturing or formulation changes are made for products containing complex drug substances (e.g., a protein), pharmacokinetic (PK) studies comparing the product before and after the changes may be performed to ensure that the PK characteristics have not changed as a result of product changes. Although such studies are sometimes referred to as BE studies, they generally do not focus on assessing release of drug substance from drug product. Nonetheless, such studies should be reported in this section. Note also that PK studies alone may not be sufficient to assure similarity between such drug products. In many situations,

pharmacodynamic (PD) studies or clinical trials may be necessary. Additionally, depending on the circumstances, antigenicity data may also be needed. Results of these other types of studies, when they are needed, should be reported in the appropriate places in the dossier.

b) Evidence of the extent of food effects on BA and conclusions regarding BE with respect to meal type or timing of the meal (where appropriate).

c) Evidence of correlations between in vitro dissolution and BA, including the effects of pH on dissolution, and conclusions regarding dissolution specifications.

d) Comparative bioavailability, including BE conclusions, for different dosage form strengths.

e) Comparative BA of the clinical study formulations (for clinical studies providing substantial evidence of efficacy) and the formulations to be marketed.

The source and magnitude of observed inter- and intra-subject variability for each formulation in a comparative BA study.

MODULE 3: QUALITY

3.1 Table of contents of Module 3

A table of contents for the filed product dossier should be provided.

3.2 Body of data

3.2S Drug substance (or active pharmaceutical ingredient (API)

The API information can be submitted to NDA in one of the following three options:

a) Option 1: Certificate of suitability of the European Pharmacopoeia (CEP); or

b) Option 2: Active pharmaceutical ingredient pre-qualified by WHO.

c) Option 3: Full details in Section 3.

The applicant should clearly indicate at the beginning of the API section (in the PD and in the QOS-PD) how the information on the API for each API manufacturer is being submitted. The API information submitted by the applicant/ FPP manufacturer should include the following for each of the options used.

Option 1: Certificates of Suitability of the European Pharmacopoeia (CEP)

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

In addition, a written commitment should be included that the applicant will inform NDA in the event that the CEP is withdrawn. It should also be acknowledged by the applicant that withdrawal of the CEP will require additional consideration of the API data requirements to support the PD. The written commitment should accompany the copy of the CEP in Module 1.

Along with the CEP the applicant should supply the following information in the dossier, with data summarized in the QOS-PD.

a) 3.2.S.1.3 General properties - discussions on any additional applicable physicochemical and other relevant API properties that are not controlled by the CEP and Ph. Eur. monograph, e.g. solubilities and polymorphs as per guidance in this section.

b) 3.2.S.3.1 Elucidation of structure and other characteristics - studies to identify polymorphs (exception: where the CEP specifies a polymorphic form) and particle size distribution, where applicable, as per guidance in this section.

c) 3.2.S.4.1 Specification - the specifications of the FPP manufacturer including all tests and limits of the CEP and Ph. Eur. monograph and any additional tests and acceptance criteria that are not controlled in the CEP and Ph. Eur. monograph, such as polymorphs and/or particle size distribution.

d) 3.2.S.4.2/3.2.S.4.3 Analytical procedures and validation - for any tests in addition to those in the CEP and Ph. Eur. monograph.

e) 3.2.S.4.4 Batch analysis - results from two batches of at least pilot scale, demonstrating compliance with the FPP manufacturer's API specifications.

f) 3.2.S.5 Reference standards or materials - information on the FPP manufacturer's reference standards.

g) 3.2.S.6 Container-closure system - specifications including descriptions and identification of primary packaging components.

h) 3.2.S.7 Stability - exception: where the CEP specifies a re-test period that is the same as or of longer duration than the re-test period proposed by the applicant.

In the case of sterile APIs, data on the sterilization process of the API, including validation data, should be included in the PD.

Option 2: Active pharmaceutical ingredient pre-qualified by WHO

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

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

a) 3.2.S.1.3 General properties - discussions on any additional applicable physicochemical and other relevant API properties that are not controlled by the API manufacturer's specifications, e.g. solubilities and polymorphs according to the guidance in this section.

b) 3.2.S.2 - if the sterility of the FPP is based upon the sterile manufacture of the API then data on the sterilization process together with full validation data should be provided.

c) 3.2.S.3.1 Elucidation of structure and other characteristics - studies to identify polymorphs and particle size distribution, where applicable, according to the guidance in this section.

d) 3.2.S.4.1 Specification - the specifications of the FPP manufacturer including all tests and limits of the API manufacturer's specifications and any additional tests and acceptance criteria that are not controlled by the API manufacturer's specifications such as polymorphs and/or particle size distribution.

e) 3.2.S.4.2/3.2.S.4.3 Analytical procedures and validation - any methods used by the FPP manufacturer in addition to those in the API manufacturer's specifications.

f) 3.2.S.4.4 Batch analysis - results from two batches of at least pilot scale, demonstrating compliance with the FPP manufacturer's API specifications.

g) 3.2.S.5 Reference standards or materials - information on the FPP manufacturer's reference standards.

h) 3.2.S.7 Stability - data to support the retest period if either the proposed retest period is longer or the proposed storage conditions are at a higher temperature or humidity to that of the prequalified API.

Option 3: Full details in the PD

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 PD as outlined in the subsequent sections of this guideline.

3.2S.1 General information (name, manufacturer)

3.2S.1.1 Nomenclature (name, manufacturer)

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

a) (Recommended) International Nonproprietary Name (INN);

b) Compendial name, if relevant;

c) Chemical name(s);

d) Company or laboratory code;

e) Other nonproprietary name(s) (e.g., national name, United States Adopted Name (USAN)

f) Adopted Name

i. (USAN), British Approved Name (BAN)); and

ii. 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.

3.2S.1.2 Structure (name, manufacturer)

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.

3.2S.1.3 General Properties (name, manufacturer)

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 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-PD). This list is not intended to be exhaustive, but provides an indication as to the type of information that could be included.

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

Physical description

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

Solubilities/quantitative aqueous pH solubility profile

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

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

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

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

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

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

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

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

Polymorphism

a) The polymorphic form(s) present in the proposed API should be listed in section 3.2.S.1.3;

b) The description of manufacturing process and process controls (3.2.S.2.2) should indicate which polymorphic form is manufactured, where relevant; the literature references or studies performed to identify the potential polymorphic forms of the API, including the study results, should be provided in section 3.2.S.3.1; and

c) 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.

3.2S.2 Manufacture (name, manufacturer)

3.2S.2.1 Manufacturer(s) (name, manufacturer)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

The 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), this 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 PD in Module 1.

3.2S.2.2 Description of manufacturing process and process controls (name, manufacturer) 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 third 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.

3.2S.2.3 Control of materials (name, manufacturer)

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 PD should:

a) 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;

b) be a well characterized, isolated and purified substance with its structure fully elucidated including its stereochemistry (when applicable);

c) 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

d) d) 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.

When available, a CEP demonstrating TSE-compliance should be provided. A complete copy of the CEP (including any annexes) should be provided in Module l.

3.2S.2.4 Controls of critical steps and intermediates (name, manufacturer)

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

3.2S.2.5 Process validation and/or evaluation (name, manufacturer)

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.

3.2S.3 Characterization (name, manufacturer)

3.2S.3.1 Elucidation of structure and other characteristics (name, manufacturer)

Confirmation of structure based on e.g. synthetic route and spectral analyses should be provided. Information such as the potential for isomerism, the identification of stereochemistry or the potential for forming polymorphs should also be included.

Elucidation of structure

The PD should include quality assurance (QA) certified copies of the spectra, peak assignments and a detailed interpretation of the data of the studies performed to elucidate and/or confirm the structure of the API. The QOS-PD 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 (XRPD) and differential scanning calorimetry (DSC).

For APIs that are described in an officially recognized pharmacopoeia, it is generally sufficient to provide copies of the IR spectrum of the API from each of the proposed manufacturer(s) 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 identicality 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 interconversion of the isomers in the isomeric mixture, or racemisation 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. Any unexpected inclusion or exclusion of a particular polymorph of the API 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. XRPD 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.

3.2S.3.2 Impurities (name, manufacturer)

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, Q3B 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.

3.2S.4 Control of the API (name, manufacturer)

3.2S.4.1 Specification (name, manufacturer)

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 PD, including specifications from each API manufacturer as well as those of the FPP manufacturer.

The FPP manufacturer's API specification should be summarized according to the table in the QOS-PD template under the headings tests, acceptance criteria and analytical procedures (including types, sources and versions for the methods).

a) The standard declared by the applicant could be an officially recognized compendial standard (e.g. BP, Ph. Eur., Ph. Int., 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 (e.g. BP, 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.

3.2S.4.2 Analytical procedures (name, manufacturer)

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.

3.2S.4.3 Validation of analytical procedures (name, manufacturer)

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-PD. 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-PD.

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 Validation 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.

3.2S.4.4 Batch analyses (name, manufacturer)

Description of batches and results of batch analyses should be provided.

The information provided should include batch number, batch size, date and production site of relevant API batches.

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-PD.

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).

3.2S.4.5 Justification of specification (name, manufacturer)

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.

3.2S.5 Reference standards or materials (name, manufacturer)

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 (e.g. BP, 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).

3.2S.6 Container-closure system (name, manufacturer)

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

3.2S.7 Stability

Refer to Appendix 10 - *Guidelines on Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products*

3.2P Drug product (or finished pharmaceutical product (FPP)) (name, dosage form)

3.2P.1 Description and Composition of the FPP (name, dosage form)

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

a) 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.

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

The tables in the QOS-PD 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 (e.g. BP, 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.

c) Description of accompanying reconstitution diluent(s)

For FPPs supplied with reconstitution diluent(s), information on the diluent(s) should be provided in a separate FPP portion ("3.2.P"), as appropriate.

3.2P.2 Pharmaceutical development (name, dosage form)

The Pharmaceutical development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing

process, container-closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the product dossier. 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) 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.

References:

a) ICH Q8 guidelines: Pharmaceutical Development

b) ICH Q9 guidelines: Quality Risk Management

3.2P.2.1 Components of the FPP (name, dosage form)

3.2P.2.1.1 active pharmaceutical ingredient (name, dosage form)

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.

3.2P.2.1.2 Excipients (name, dosage form)

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.

3.2P.2.2 Finished pharmaceutical product (name, dosage form)

3.2P.2.2.1 Formulation development (name, dosage form)

A brief summary describing the development of the FPP should be provided, taking into consideration the proposed route of administration and usage. The differences between the comparative bioavailability or biowaiver formulations and the formulation (i.e. composition) described in 3.2.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.

3.2P.2.2.2 Overages (name, dosage form)

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).

3.2P.2.2.3 Physicochemical and biological properties (name, dosage form)

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.

3.2P.2.3 Manufacturing process development (name, dosage form)

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 sterilisation 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.

3.2P.2.4 Container-closure system (name, dosage form)

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.

3.2P.2.5 Microbiological attributes (name, dosage form)

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

Where an antimicrobial preservative is included in the formulation, the amount used should be justified by submission of results of the product formulated with different concentrations of the preservative(s) to demonstrate the least necessary but still effective concentration. The effectiveness of the agent should be justified and verified by appropriate studies (e.g. USP or Ph.Eur. general chapters on antimicrobial preservatives) using a batch of the FPP. If the lower 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.

3.2P.2.6 Compatibility (name, dosage form)

The compatibility of the FPP with reconstitution diluent(s) or dosage devices (e.g. precipitation of API in solution, sorption on injection vessels, stability) should be addressed to provide appropriate and supportive information for the 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.

3.2P.3 Manufacture (name, dosage form)

3.2P.3.1 Manufacturer(s) (name, dosage form)

The name, address and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

The facilities involved in the manufacturing, packaging, labelling and testing should be listed. If certain companies are responsible only for specific steps (e.g. manufacturing of an intermediate) this 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 that the product is registered or licensed in accordance with national Regulatory 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, this product has been withdrawn from the market and/ or this application for marketing has been rejected, deferred or withdrawn. This information should be submitted in section 1.9.

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

A batch formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages, and a reference to their quality standards.

The tables in the QOS-PD template should be used to summarize the batch formula of the FPP for each proposed commercial batch size and express the quantity of each component on a per batch basis, including a statement of the total weight or measure of the batch.

All 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, 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).

3.2P.3.3 Description of manufacturing process and process controls (name, dosage form)

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

A narrative description of the manufacturing process, including packaging that represents the sequence of steps undertaken and the scale of production should also be provided. Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater level of detail. Equipment should, at least, be identified by type (e.g. tumble blender, inline 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.

3.2P.3.4 Controls of critical steps and intermediates (name, dosage form)

Critical steps: tests and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps identified in 3.2.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.

3.2P.3.5 Process validation and/or evaluation (name, dosage form)

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

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) If the process validation studies have already been conducted (e.g. for sterile products), a copy of the process validation report should be provided in the PD in lieu of (a) and (b) above.

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 time frame 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 (refer to Annex 11 - Product Quality Review Requirements for Generic Pharmaceutical Products) 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.

3.2P.4 Control of excipients (name, dosage form)

3.2P.4.1 Specifications (name, dosage form)

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 NDA by the applicant 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.

3.2P.4.2 Analytical procedures (name, dosage form)

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

3.2P.4.3 Validation of analytical procedures (name, dosage form)

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

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.

3.2P.4.4 Justification of specifications (name, dosage form)

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.

3.2P.4.5 Excipients of human or animal origin (name, dosage form)

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

3.2P.4.6 Novel excipients (name, dosage form)

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

3.2P.5 Control of FPP (name, dosage form)

3.2P.5.1 Specification(s) (name, dosage form)

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- PD 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.

3.2P.5.2 Analytical procedures (name, dosage form)

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.

3.2P.5.3 Validation of analytical procedures (name, dosage form)

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 PD) 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.

3.2P.5.4 Batch analyses (name, dosage form)

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 two batches of which at least one should be of commercial scale and two pilot scale batches.

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 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).

3.2P.5.5 Characterization of impurities (name, dosage form)

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).

3.2P.5.6 Justification of specification(s) (name, dosage form)

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 PD and does not need to be repeated here, although a cross-reference to their location should be provided.

3.2P.6 Reference standards or materials (name, dosage form)

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

3.2P.7 Container-closure system (name, dosage form)

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

3.2P.8 Stability

Refer to Appendix 10 - *Guidelines on Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products*

3.2R Regional information

3.2R.1 Production documents

3.2R.1.1 Executed production documents

A minimum of two batches of at least pilot scale, or in the case of an uncomplicated FPP (e.g. immediate-release solid FPPs (with noted exceptions) or non-sterile solutions), at least one batch of at least pilot scale (the batch used in comparative bioavailability or biowaiver studies) and a second batch which may be smaller (e.g. for solid oral dosage forms, 25 000 or 50 000 tablets or capsules), should be manufactured for each strength. These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

For solid oral dosage forms, pilot scale is generally, at a minimum, one-tenth that of full productio9n scale or 100,000 tablets or capsules, whichever is the larger.

Copies of the executed production documents should be provided for the batches used in the comparative bioavailability or bio-waiver studies. Any notations made by operators on the executed production documents should be clearly legible.

If not included in the executed batch records through sufficient in-process testing, data should be provided for the batch used in comparative bioavailability or bio-waiver studies that demonstrate the uniformity of this batch. The data to establish the uniformity of the bio-batch should involve testing to an extent greater than that required in routine quality control.

English translations of executed records should be provided where relevant.

3.2R.1.2 Master production documents

Copies of the FPP master production documents should be provided for each proposed strength, commercial batch size and manufacturing site.

The details in the master production documents should include, but not be limited to, the following:

a) master formula;

b) dispensing, processing and packaging sections with relevant material and operational details;

c) relevant calculations (e.g. if the amount of API is adjusted based on the assay results or on the anhydrous basis);

d) identification of all equipment by, at a minimum, type and working capacity (including make, model and equipment number, where possible);

e) process parameters (e.g. mixing time, mixing speed, milling screen size, processing temperature range, granulation end-point and tablet machine speed (expressed as target and range);

f) list of in-process tests (e.g. appearance, pH, assay, blend uniformity, viscosity, particle size distribution, loss on drying, weight variation, hardness, disintegration time, weight gain during coating, leaker test, minimum fill, clarity and filter integrity checks) and specifications;

g) sampling plan with regard to the:

i. steps at which sampling should be done (e.g. drying, lubrication and compression),

ii. number of samples that should be tested (e.g. for blend uniformity testing of low-dose FPPs, blend drawn using a sampling thief from x positions in the blender),

iii. frequency of testing (e.g. weight variation every x minutes during compression or capsule filling);

h) precautions necessary to ensure product quality (e.g. temperature and humidity control and maximum holding times);

i) for sterile products, reference to standard operating procedures (SOPs) in appropriate sections and a list of all relevant SOPs at the end of the document;

j) theoretical and actual yield;

k) compliance with the GMP requirements.

3.2R.2 Analytical procedures and validation information

The tables presented in section 2.3.R.2 in the QOS-PD template should be used to summarize the analytical procedures and validation information from sections 3.2.S.4.2, 3.2.S.4.3, 2.3.S.4.4 (c), 2.3.S.7.3 (b), 3.2.P.5.2 and 3.2.P.5.3 where relevant.

3.3 Literature references

References to the scientific literature relating to both the API and FPP should be included in this section of the PD when appropriate.

MODULE 4: NON CLINICAL STUDY REPORTS

Generic products are generally exempted in this module.

In case of products containing new active ingredients and new combinations of active ingredients provide full information on Non Clinical Study Reports as defined in relevant current ICH guidelines.

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

5.3.1 Reports of Biopharmaceutic Studies

5.3.1.1 Bioavailability (BA) Study Reports

5.3.1.2 Comparative BA and Bioequivalence (BE) Study reports

Refer to Appendix 12 - *Guidelines on therapeutic equivalence requirements and Appendix 13 Guidelines for application of biopharmaceutical classification system biowaivers*

In case a biowaiver is applicable the applicant must complete the *Biowaiver Application Form* (Appendix 14).

5.3.1.3 In vitro-In vivo Correlation Study Reports

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

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

5.3.7 Case Report Forms and Individual Patient Listings

6.0 References

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WHO good distribution practices for pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth report. Geneva, World Health Organization, 2010, Annex 5 (WHO Technical Report Series, No. 957).

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WHO Guidelines on development of paediatric medicines: points to consider in formulation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty- sixth report. Geneva, World Health Organization, 2012, Annex 5 (WHO Technical Report Series, No. 970).

APPENDIX 1: FORMAT FOR CTD COVER LETTER

Ref: .....

Applicant: .....

Address: .....

Post code: ..... Town ..... Country: .....

Date: .....

Reference: .....

The Secretary to the Authority,

National Drug Authority, Plot 19 Lumumba Avenue
P.O. Box 23096, Kampala, Uganda
Phone: (+256) 41-7788100
E-mail: ndaug@nda.or.ug

Subject: Submission of Application(s) for Registration of Product Name(s) and strength(s)

Dear Sir,

We are pleased to submit our Application(s) for a registration of finished pharmaceutical product(s) whose details are as follows:

Name of the finished pharmaceutical product(s): .....

Pharmaceutical form(s) and strength(s): .....

INN/active substance(s): ..... ATC Code(s): .....

You will find enclosed the submission dossier as specified hereafter:

CD rom; Quality Overall Summary and Bioequivalence Trial Information 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 an up-to-date and state-of-the-art virus checker.

The relevant fees have been paid.

Yours sincerely,

Signature: .....

Name: .....

Title: .....

Phone number: .....

Email address: .....

APPLICATION FOR REGISTRATION OF A PHARMACEUTICAL PRODUCT FOR HUMAN USE IN UGANDA

Application Number	[For NDA use only]
Date of submission of the dossier	[For NDA use only]

MODULE 1: ADMINISTRATIVE INFORMATION

1.0 PARTICULARS OF THE PRODUCT

1.1	Type of the pharmaceutical product application Innovator: Generic Renewal* * If variation has been made, information supporting the changes should be submitted using the *Guidelines for Variation of Registered Pharmaceutical Products for Human Use.*
1.2	Proprietary Name
1.3	International Non-proprietary Name (INN) of the Active Pharmaceutical Ingredient (API)
1.4	Strength of Active Pharmaceutical Ingredient (API) per unit dosage form:
1.5	Name and address (physical and postal) of the Applicant .
(Company) Name: Address: Country: Telephone: Telefax: E-Mail:	
1.6	Pharmaceutical Dosage form and route of administration* * List of standard terms for dosage forms and routes of administration is available in the *Guidelines on Submission of Documentation for Registration of a Pharmaceutical Products for Human Use* in Uganda
1.6.1	Dosage form:
1.6.2	Route(s) of administration (use current *List of Standard Terms*)
1.7	Packing/pack size:

1.8	Visual description *(Add as many rows as necessary)*
1.9	Proposed shelf life (in months):
1.9.1	Proposed shelf life (after reconstitution or dilution):
1.9.2	Proposed shelf life (after first opening container):
1.9.3	Proposed storage conditions:
1.9.4	Proposed storage conditions after first opening:
1.10	Other sister pharmaceutical products registered or applied for registration
1.10.1	Do you hold a certificate (s) of registration for other pharmaceutical product (s) containing the same active substance (s) in the Uganda? If yes state; ▪ Product name (s), strength (s), pharmaceutical form (s): ▪ Registration number(s): ▪ Indication(s):
1.10.2	Have you applied for registration of pharmaceutical product (s) containing the same active substance (s)? ▪ Product name (s), strength (s), pharmaceutical form (s): ▪ Indication(s):
1.11	Pharmacotherapeutic group and ATC Code
1.11.1	Pharmacotherapeutic group:
1.11.2	ATC Code: (*Please use current ATC code)*
1.11.3	If no ATC code has been assigned, please indicate if an application for ATC code has been made: ☐
1.12	Distribution category: Controlled Drug ☐ POM ☐ Pharmacy Only ☐ OTC ☐ General sale ☐ *(Applicants are invited to indicate which categories they are requesting, however, NDA reserves the right to change and/or apply only those categories provided for in their national legislation)*
1.13	Country of origin:
1.14	Product Marketing Authorisation in the country of origin (Attach Certificate of Pharmaceutical Product). If not registered, state reasons

☐ **Authorised** Country: Date of authorisation (dd-mm-yyyy): Proprietary name: Authorisation number: ☐ **Refused** Country: Date of refusal (dd-mm-yyyy): Reason for Refusal:	☐ **Withdrawn** (by applicant after authorisation) Country: Date of withdrawal (dd-mm-yyyy): Proprietary name: Reason for withdrawal: ☐ **Suspended/revoked** (by competent authority) Country: date of suspension/revocation (dd-mm-yyyy): Reason for suspension/revocation: Proprietary name:

1.15	List EAC countries and SRAs where the product is approved.
1.16	Name(s) and complete physical address(es) of the manufacturer(s)
1.16.1	Name(s) and physical address(es) of the manufacturing site of the finished pharmaceutical product (FPP), including the final product release if different from the manufacturer**.** Alternative sites should be also declared here**.** *All manufacturing sites involved in the manufacturing process of each step of the finished product, stating the role of each including quality control / in-process testing sites should be listed.* (Add as many rows as necessary)

Name:

Company name:

Address:

Country:

Telephone:

Telefax:

E-Mail:

1.16.2	Name(s) and physical address(es) of the manufacturer(s) of the active pharmaceutical ingredient(s) (API) *(Add as many rows as necessary)* *All manufacturing sites involved in the manufacturing process of each source of active substance, including quality control / in-process testing sites should be listed.*
Name: Company name: Address: Country: Telephone: Telefax: E-Mail:	
1.17	Name and address (physical and postal) of the Local Technical Representative / agent(Attach acopy of Notarised power of attorney for the local technical representative /agent)*if applicable)*
Name: Company name: Address: Country: Telephone: Telefax: E-Mail:	
1.18	Name and address (physical and postal) of the person or company responsible for pharmacovigilance
Name: Company name: Address: Country: Telephone:	

Telefax: E-Mail:	
1.19	State the reference/monograph standard such as British Pharmacopeia, United States Pharmacopeia, Ph. Eur., In-house monograph e.t.c. used for Finished Pharmaceutical Product.
1.20	Qualitative and Quantitative composition of the active substance(s) and excipient(s) *A note should be given as to which quantity the composition refers (e.g. 1 capsule).*

Name of active ingredient(s)*	Quantity / dosage unit	Unit of measure	Reference/ Monograph standard	
1.				
2.				
3.				
e.t.c				
Name Excipient(s)				
1.				
2.				
3				
e.t.c				

Note:

** Only one name for each substance should be given in the following order of priority: INN**, Pharmacopoeia, common name, scientific name*

*** The active substance should be declared by its recommended INN, accompanied by its salt or hydrate form if relevant. Details of averages should not be included in the formulation columns but should be stated below:*

- Active substance(s):
- Excipient(s):

1.21	Name and address (physical and postal) of the Contract Research Organisation(s) where the clinical studies of the product were conducted. *(If applicable)*

Name:

Company name:

Address:

Country:

Telephone:

Telefax:

E-Mail:

2.0 DECLARATION BY AN APPLICANT

I, the undersigned certify that all the information in this form and accompanying documentation is correct, complete and true to the best of my knowledge.

I further confirm that the information referred to in my application dossier is available for verification during GMP inspection.

I also agree that I shall carry out pharmacovigilance to monitor the safety of the product in the market and provide safety update reports to the National Drug Authority.

I further agree that I am obliged to follow the requirements of the National Drug Authority.

Legislations and Regulations which are applicable to pharmaceutical products.

It is hereby confirmed that fees will be paid/have been paid according to the national/

Community rules*

Name: ……..…….

Position in the company:……

Signature: ……..……

Date:……..

Official stamp:……..

** Note: If fees have been paid, attach proof of payment*

APPENDIX 2: STANDARD FORMAT FOR QUALITY INFORMATION SUMMARY (QIS)

FOREWORD

The QIS template should be completed to provide a condensed summary of the key quality information for product dossiers (PDs) containing APIs of synthetic or semi-synthetic origin and their corresponding products that are filed with the Prequalification Programme.

The QIS constitutes part of the PD. The QIS provides an accurate record of technical data in the PD at the time of Marketing Authorization and thereafter serves as an official reference document during the course of GMP inspections, variation assessments and renewal of Marketing Authorizations by NDA. The QIS is a condensed version of the Quality Overall Summary – Product Dossier (QOS-PD) and represents the final, agreed upon key information from the PD review (inter alia identification of the manufacturer(s), API/FPP specifications, stability conclusions and relevant commitments).

The QIS template is structured to permit the rapid assembly of the QIS by copying requisite information from the corresponding portions of the QOS-PD filed with the original PD. It is acknowledged that the numbering of the sections may not be entirely sequential. Those sections not considered necessary to be included in the QIS have been removed (e.g. *2.3.S.5 Reference Standards or Materials*) and the remaining sections have retained their numbering to be consistent with the original PD.

For original PDs, the QIS should be provided in Word format at the time of PD submission. The QIS should be revised and submitted with the change history (see table at the end of the template) each time additional data is provided during the assessment process. If no revision is necessary due to no change in the information, a statement should be made to this effect in the covering letter. For variations and requalification dossiers, the QIS should be completed *in its entirety* (regardless of the proposed change), it should include information on *all strengths*, with any changes highlighted and it should be provided *at the time of filing*.

When completing the QIS template, this covering foreword should be deleted.

INTRODUCTION

(a) Summary of product information:

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

(b) Administrative Summary:

Applicant's date of preparation or revision of the QIS	
Internal version and/or date of acceptance	*(NDA use only)*

Related dossiers (e.g. FPP(s) with the same API(s) submitted to the Pre-qualification Programme by the applicant):

Reference/ File *number (e.g. J998)*	**Registration granted (Y/N)**	**API, strength, dosage form** *(e.g. Abacavir (as sulphate) 300 mg tablets)*	**API manufacturer** *(including address)*

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

Indicate which option applies for the submission of API information:

Name of API:	
Name of API manufacturer	
a)	Certificate of suitability to the European Pharmacopoeia (CEP)?
b)	API prequalified by WHO
c)	Full details in the PD

2.3.S.2 Manufacture (name, manufacturer)

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

(a) Name, address and responsibility (e.g. fabrication, packaging, labelling, testing, and 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	API-PQ number /APIMF/CEP number (if applicable)	Letter of access provided?

2.3.S.2.3 Control of Materials (name, manufacturer)

(a) Name of starting material:

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

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

2.3.S.4.1 Specification (name, manufacturer)

(a) API specifications of the FPP manufacturer:

Standard (e.g. Ph.Int., Ph.Eur., BP, USP, In-House)	
Specification reference number and version	

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

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

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

2.3.S.7 Stability (name, manufacturer)

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

(a) Proposed storage conditions and re-tests period:

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)

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

2.3.P.1 Description and Composition of the FPP

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

(b) Composition of the FPP:

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

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

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

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

2.3.P.2.2.1 Formulation Development

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

(i) Summary of batch numbers:

Batch number(s) of the FPPs used in	
Bioequivalence or biowaiver	
For proportional strength biowaiver: the bioequivalence batch of the reference strength	
Dissolution profile studies	

Stability studies (primary batches)			
‹packaging configuration I›			
‹ packaging configuration II›			
‹*Add/delete as many rows as necessary*›			
Stability studies (production batches)			
‹ packaging configuration I›			
‹ packaging configuration II›			
(Add/delete as many rows as necessary)			
Validation studies (primary batches)			
‹ packaging configuration I›			
‹ packaging configuration II›			
(Add/delete as many rows as necessary)			
Validation studies (at least the first three consecutive production batches) **or code(s)/version(s) for process validation protocol(s)**			

Summary of formulations and discussion of any differences:

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

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

2.3.P.3 Manufacture

2.3.P.3.1 Manufacturer(s)

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

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

2.3.P.3.2 Batch Formula

Largest intended commercial batch size:

Other intended commercial batch sizes:

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

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

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

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

(a) Flow diagram of the manufacturing process:

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

2.3.P.3.4 Controls of Critical Steps and Intermediates

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

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

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

2.3.P.3.5 Process Validation and/or Evaluation

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

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

2.3.P.5 Control of FPP

2.3.P.5.1 Specification(s)

(a) Specification(s) for the FPP:

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

2.3.P.7 Container Closure System

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

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

2.3.P.8 Stability

2.3.P.8.1 Stability Summary and Conclusions

(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)	*<primary batches>*	
Tests and acceptance criteria	Description	
	Moisture	
	Impurities	
	Assay	
	etc.	
Testing frequency		
Container closure system(s)		

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

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

Parameter	Details
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) (ºC, % 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

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

WRITTEN COMMITMENTS OF THE MANUFACTURER – NDA use

API

If applicable (primary stability study commitment):

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

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

If applicable (commitment stability studies):

Since stability data on three production scale batches were not provided with the application, the remaining number of production scale batches should be put on long-term stability testing. Any significant changes or out-of-specification results should be reported immediately to NDA. The approved stability protocol should be used for commitment batches.

API option 2 - CEP

The Applicant provided a commitment in writing (date of letter of commitment) to inform NDA in the event that the CEP is withdrawn. Note that withdrawal will require additional consideration of the API data requirements to support the dossier.

API option 3 - full details in the PD (ongoing stability study commitment)

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

FPP

If applicable (primary stability study commitment):

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

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

If applicable (commitment stability studies):

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

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

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

Ongoing stability study commitment

The Applicant undertook in writing (date of letter of commitment) a commitment regarding ongoing stability studies. Unless otherwise justified, at least one batch per year of the product manufactured in every primary packaging type will be included in the stability programme (unless none is produced during that year). The stability protocol will be that which was approved for primary batches (or the protocol was submitted for assessment). 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 NDA. The possible impact on batches on the market should be considered in consultation with NDA inspectors.

If applicable (validation of production batches)

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

Change History

Date of preparation of original QIS:

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

APPENDIX 3: GUIDELINES ON FORMAT AND CONTENT OF SUMMARY OF PRODUCT CHARACTERISTICS FOR PHARMACEUTICAL PRODUCTS

INTRODUCTION

The Summary of Product Characteristics (SmPC) sets out the agreed position of the finished pharmaceutical product as distilled during the course of the assessment process. As such the content cannot be changed except with the approval of the national medicines regulatory authority.

The SmPC is the basis of information for healthcare professionals on how to use the finished pharmaceutical product safely and effectively.

This guideline provides advice on the principles of presenting information in the SmPC. Applicants should maintain the integrity of each section of the document by only including information in each section which is relevant to the section heading. However, some issues may need to be addressed in more than one section of the SmPC and in such situations the individual statements may cross-refer to other sections when these contain relevant additional information.

Separate SmPCs are required for each pharmaceutical form and strength.

Principles of presenting information

a) The SmPC should be worded in clear and concise language.

b) 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).

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

d) The SmPC provides information on a particular finished pharmaceutical product, therefore, it should not include reference to other finished pharmaceutical 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.

SMPC Format and Content

The SmPC will be structured and populated as outlined in 1-12 below.

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

The proprietary name should be followed by both the strength and the pharmaceutical form. However, when otherwise referring to the finished pharmaceutical 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.

1.1. 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 finished pharmaceutical 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 finished pharmaceutical 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.

1.2. Pharmaceutical form

The pharmaceutical form of a finished pharmaceutical product should be described by a standard term (refer to the List of Standard Terms for Pharmaceutical Dosage Forms and Routes of Administration). 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) and excipients, knowledge of which are essential for proper administration of the finished pharmaceutical 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 (refer to the Guidelines on Format and Content of Labels for Pharmaceutical Products) 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 of excipients, see section 6.1’.

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

2.1. Qualitative declaration

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

2.2. Quantitative declaration

The quantity of the active substance should be expressed per dosage unit (for metered dose inhalation products, per delivered dose and/or per metered dose), per

unit volume, or per unit of weight and should be related to the declaration of strength in section 1.

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

2.3. Salts and hydrates

Where the active substance is present in the form of a salt or hydrate, the quantitative composition should be expressed in terms of the mass (or biological activity in International (or other) units where appropriate) 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 the mixture of a solvent and powder), the quantity of the active moiety should be stated, with a reference to the in situ formation of the salt.
In the case of established active substances in finished pharmaceutical products where the strength has traditionally been expressed in the form of a salt or hydrate, the quantitative composition may be declared in terms of the salt or hydrate, e.g. '60 mg diltiazem hydrochloride'. This may also apply when the salt is formed in situ.

2.4. Esters and pro-drugs

If the active substance is an ester or pro-drug, the quantitative composition should be stated in terms of the quantity of the ester or pro-drug. When the active moiety is an active substance of an already approved finished pharmaceutical 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).

2.5. Oral powders for solution or suspension

The quantity of active substance should be stated per unit dose if the product is a singledose preparation or otherwise per unit dose volume after reconstitution; a reference to the molar concentration may also be appropriate in some cases.

2.6. Parenterals excluding powders for reconstitution

For single-dose parenterals, where the total contents of the container are given in a single dose ('total use'), the quantity of active substance(s) should be stated per presentation (e.g. 20 mg etc.) not including 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's weight or body surface or other variable ('partial use'), the quantity of active substance(s) should be stated 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 per ml, per 100 ml, per 1000 ml, etc. as appropriate, except for

multidose vaccines containing 'n' doses of the same dose. In this case, the strength should be expressed per dose volume. Overages or overfills should not be included.

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

2.7. Powders for reconstitution prior to parenteral administration

When the product is a powder to be reconstituted prior to administration, the total quantity of active substance in the container should be stated not including overages or overfills, as well as the quantity per ml when reconstituted, unless there are several means of reconstituting, or different quantities used, which result in different final concentrations.

2.8. Concentrates

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

2.9. Transdermal patches

The following quantitative details should be given: the content of active substance(s) per patch, the mean dose delivered per unit time, and the area of the releasing surface, e.g. 'Each patch contains 750 micrograms of estradiol in a patch size of 10 cm^2, releasing a nominal 25 micrograms of estradiol per 24 hours'.

2.10. 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.

2.11. Biological medicinal products

2.11.1. 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.

2.11.2. 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:

a) “produced in human diploid (MRC-5) cells”;

b) “produced in Escherichia coli cells by recombinant DNA technology”;

c) “produced in chick-embryo cells”;

d) “produced from the plasma of human donors”;

e) “produced from human urine”;

f) “produced from <animal>blood”;

g) “produced from porcine pancreatic tissue”;

h) “produced from porcine intestinal mucosa”.

2.11.3. 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.

2.11.4. Herbal pharmaceutical products

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

3. PHARMACEUTICAL FORM

The pharmaceutical form should be stated 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 osmolarity 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 4.2 and 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 authorised 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 adult 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 available").

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/m2) 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:

a) the maximum recommended single, daily and/or total dose;

b) the need for dose titration;

c) the normal duration of use and any restrictions on duration and, if relevant, the need for tapering off, or advice on discontinuation;

d) 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);

e) advice on preventive measures to avoid certain adverse drug reactions (e.g. administration of antiemetics) with cross-reference to section 4.4;

f) 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;

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

h) 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

i) 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:

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

b) 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;

c) 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;

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

e) 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/m2) 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 newborns 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 summarised 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 have not yet been established.

One of the following statements should be added:

i. No data is available or

ii. Currently available data is described in section 4.8, 5.1, 5.2 but no recommendation on a posology can be made

a) 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)

b) 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)

c) Specify indication(s).

d) 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.

4.3. 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 subheading (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 section 6.6 ‘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, pulverising 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.:

a) “the coated tablet should not be chewed because of bad taste,

b) “the enteric-coated tablet should not be crushed because coating prevents pH sensitive degradation irritant effects on the gut”,

c) “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”).

4.4. 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 pharmaceutical 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.

4.5. 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:

a) 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 minimisation 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”)

b) 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 anaesthesic 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.

c) 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.

d) 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.

e) 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.

f) 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.

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

h) 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.

i) Any warnings necessary with respect to transmissible agents

j) Subjects or patients with a specific genotype or phenotype might either not respond to the treatment or be at risk of a pronounced pharmacodynamic 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.

k) 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 breastfeeding, ability to drive and use machines, and other aspects of interactions should be dealt with in sections 4.6, 4.7 and 4.5, 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.

4.6. 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.

4.7. 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 pharmacodynamic 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:

i. contraindications of concomitant use (cross-refer to section 4.3),

ii. concomitant use not recommended (cross-refer to section 4.4), and

iii. 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 summarised.

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 pharmacodynamic 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.

4.8. 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 metabolising enzymes or certain genotypes, this should be stated.

4.9. 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;

a) 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),

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

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

d) If this is not known, this should also be stated. The same applies to pharmacodynamic 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.

4.10. Fertility, pregnancy and lactation

4.10.1. General principles

Efforts should be made by the Applicant or Holder of a Certificate of Registration 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:

4.10.2. Women of childbearing potential I 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.

4.10.3. Pregnancy

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

With respect to non-clinical data,

a) 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,

b) the section should include comprehensive information on relevant adverse events reported in the embryo, the fetus, neonates and pregnant women, when appropriate. The frequency of such events (for example the frequency of birth defects) should be specified when available.

c) 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 fetal ultrasound, specific biological or clinical surveillance of the fetus or the neonate) should be given.

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

4.10.4. 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.

4.10.5. 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.

4.11. Effects on ability to drive and use machines

On the basis of the pharmacodynamic and pharmacokinetic 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).

4.12. Undesirable effects

This section should include all adverse reactions from clinical trials, post-authorisation 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 application for registration 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:

i. Summary of the safety profile
ii. Tabulated summary of adverse reactions
iii. Description of selected adverse reactions
iv. Paediatric population
v. 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 minimisation 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-authorisation 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" 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.

c) Description of selected adverse reactions

This section should include information characterising 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 characterising 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.

d) 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 summarised, 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-authorisation 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 pharmaceutical 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).

4.13. Overdose

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

Taking into account all relevant evidence, describe management of overdose in man, e.g. in relation to monitoring or use of specific agonists/antagonists, antidotes or methods to increase elimination of the medicinal product such as dialysis. However, there should not be any dosage recommendation of other medicinal 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 renal impairment, patients with hepatic impairment, other concomitant diseases etc.

Paediatric population

If there are specific paediatric considerations, there should be a sub-section entitled ‘paediatric population’.

Special mention should be made of those medicinal products/strength of formulation for which ingestion 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 in relation to the paediatric population.

Pharmacodynamic properties Describe:

a) Pharmacotherapeutic group and ATC code:

Inclusion of the therapeutic subgroup (2nd level of WHO classification) with the 3rd level (pharmacological subgroup) and the 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 authorised as similar biological medicinal product, the following statement will be included:

i. (Proprietary) Name is a biosimilar pharmaceutical product;

ii. Mechanism of action (if known);

iii. Pharmacodynamic effects;

iv. 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 authorised paediatric indication, data should be presented and a cross-reference should always be made to section 4.2 and, 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 prodrug 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 body weight (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.

a) 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).

Pharmacokinetic/pharmacodynamic relationship(s)

i. Relationship between dose/concentration/pharmacokinetic parameter and effect (either true end point, validated surrogate endpoint or side effect).

ii. The population studied should be described.

Paediatric population

Results of pharmacokinetic studies in the different paediatric age groups should be summarised, with a comparison to adults if available. If appropriate, the dose producing similar product exposure as in adults 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 recognising the safety profile of the medicinal product used for the authorised 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:

a) 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.

b) 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.

c) 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 Pharmaceutical 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 recognized 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, the excipients 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:

a) ‘In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.’

b) ‘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 development studies 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°C and 2-8 °C”.

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 or patients, 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 a 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 (chlorobutyl rubber) 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 recommended 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. HOLDER OF A CERTIFICATE OF REGISTRATION AND MANUFACTURING SITE ADDRESSES

Name and permanent address or registered place of business of the Holder of a Certificate of Registration and manufacturing site(s) physical address.

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

8. REGISTRATION NUMBER

Item to be completed by the Holder of a Certificate of Registration once the Registration has been granted by NDA

9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION

Item to be completed by the Holder of a Certificate of Registration once the Registration has been granted or renewed.

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

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

10. DATE OF REVISION OF THE TEXT

Leave blank in case of a first registration.

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.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

<text> signifies text to be selected or deleted as appropriate.

{text} refers to information to be added]

1. NAME OF THE MEDICINAL PRODUCT

   {(Invented) name strength pharmaceutical form}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

   <Excipient(s):>

   For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

   <The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.>

   <The tablet can be divided into equal halves>

   <The tablet should not be divided>

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

   <{X} is indicated in <adults> <neonates> <infants> <children> <adolescents> <aged {x to y}> <years> <months>

4.2. Posology and method of administration

   Posology

   Paediatric population

   <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>

   <No data are available.> <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)>

   <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>

<{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...> (see Section 4.3)>

Method of administration

4.3. Contraindications

<Hypersensitivity to the active substance(s) or to any of the excipients <or {name of the residue(s)}>

4.4. Special warnings and precautions for use

4.5. Interaction with other medicinal products and other forms of interaction

<No interaction studies have been performed>

<Interaction studies have only been performed in adults>

4.6. Pregnancy and lactation

<Women of childbearing potential>

<Contraception in males and females>

<Pregnancy>

<Breastfeeding>

<Fertility>

4.7. Effects on ability to drive and use machines

<{Invented name} has <no <or negligible> influence> <minor influence>, <moderate influence> <major influence> on the ability to drive and use machines.>

<No studies on the effects on the ability to drive and use machines have been performed>

<Not relevant>

4.8. Undesirable effects

<Paediatric population>

4.9. Overdose

<No case of overdose has been reported>

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: {group}, ATC code: {code}

<Mechanism of action>

<Pharmacodynamic effects>

<Clinical efficacy and safety>

<Paediatric population>

5.2 Pharmacokinetic properties

<Paediatric population>

5.3 Preclinical safety data

<Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, 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:>

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

6.2 Incompatibilities

<Not applicable.>

<In the absence of compatibility studies, this medicinal product must not be mixed with other pharmaceutical products.>

<This medicinal product must not be mixed with other medicinal products except those mentioned in Section 6.6.>

6.3 Shelf life

<6 months> <1 year> <18 months> <2 years> <30 months> <3 years>

6.4 Special precautions for storage

[For storage condition statements see NDA guidance on labelling]

<For storage conditions of the <reconstituted> <diluted> medicinal product, see Section 6.3.>

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

<Not all pack sizes may be marketed.>

6.6 Special precautions for disposal <and other handling>

<No special requirements.>

<Any unused product or waste material should be disposed of in accordance with local requirements.>

7. APPLICANT/SUPPLIER

   {Name and address}

   <{tel}>

   <{fax}>

   <{email}>

8. WHO PREQUALIFICATION REFERENCE NUMBER
9. DATE OF <PREQUALIFICATION> / <RENEWAL OF PREQUALIFICATION>

   <{DD/MM/YYYY}> <{DD month YYYY}>

10. DATE OF REVISION OF THE TEXT

    {MM/YYYY}

APPENDIX 4: GUIDELINES ON FORMAT AND CONTENT OF LABELS FOR PHARMACEUTICAL PRODUCTS

INTRODUCTION

This guideline is written to assist applicants and Holders of Certificates of Registration in drawing up the labelling and preparing the mock-ups or specimens of the sales presentations[2].

The guidance gives advice on the presentation of the content of the labelling and on the design and layout concepts which will aid the production of quality information.

Labelling covers both outer packaging and inner packaging. Although inner packaging may include a lesser set of particulars, many of the principles outlined in relation to outer packaging will apply equally to the labelling of blister packs or other small package units.

Labelling ensures that the critical information necessary for the safe use of the medicine is legible, easily accessible and that users of medicines are assisted in assimilating this information so that confusion and error are minimised.

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. 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.

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

[2] A mock-up is a copy of the flat artwork design in full colour, presented so that, following cutting and folding where necessary, it provides a replica of both the outer and immediate packaging so that the three dimensional presentation of the labelling text is clear. This mock-up is generally referred to as a paper copy and not necessarily in the material of the sales presentation. A specimen is a sample of the actual printed out outer and immediate packaging materials and package leaflet (i.e. the sales presentation).

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 Holder of a certificate of registration

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 the NDA

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

v. Note that for co-blistered products, the expiry date is that of the product which expires first[3]

vi. The batch number assigned by the manufacturer.

vii. Directions for use, and any warnings or precautions that may be necessary.

d) Labelling for transportation

A label for a package to be used to transport a drug shall include -

i. the name of the product;

ii. where applicable, a list of the active ingredients, including the International Nonproprietary Names, the amount of each active ingredient and a statement of the net content of each package, such as the number of dosage units in the package and the weight or volume of the package;

iii. the batch number of the product in the package;

iv. the expiry date of the product; and

v. the storage conditions or handling precautions required for the product;

vi. the name or trademark and the address of the manufacturer or the agent of the manufacturer.

e) Additional labelling information required by some Partner States

NDA may with time require certain additional information on labels, e.g.:

[3] The manufacturing date, if space is enough

i. Price of the medicinal product;
ii. The reimbursement conditions of social security organisations;
iii. Identification and authenticity;
iv. A statement that the product is a property of government
v. Such information should be accommodated on the label in a box, to appear on one side of the pack.

CONTROL OF THE COMFORMITY OF THE LABELING

The labelling of the pharmaceutical product forms part of the registration and it must, therefore, be approved by NDA when the registration is granted.

Any changes to the labelling, which are not connected with the Summary of Product Characteristics, shall be notified to NDA. Therefore, if a Holder of a certificate of registration wishes to either introduce any label text additional to that in the decision or to change any aspect of the labelling they must first notify this change to NDA, who shall inform the Holder of a certificate of registration whether the proposed change is accepted or not.

APPENDIX 5: GUIDELINE ON FORMAT AND CONTENT OF PATIENT INFORMATION LEAFLETS FOR PHARMACEUTICAL PRODUCTS

INTRODUCTION

The Patient Information Leaflet (PIL) is the leaflet included in the pack with a medicine. It is written for patients and gives information about taking or using a medicine. As such the content cannot be changed except with the approval of the national medicines regulatory authority.

1. GENERAL REQUIREMENTS

1.1. The Package insert

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

a) Type size and font

The following should be considered while selecting type size and font:

i. The font should be easy to read; stylized fonts which are difficult to read should not be used;

ii. The font should be such that similar letters/numbers such as “I”, “l” and “1” can be easily distinguished from each other;

iii. A minimum type size of 9 points, as measured in font ‘Times New Roman’, not narrowed, with a space between lines of at least 3 mm, should be used;

iv. Widespread use of capitals is discouraged; however, capitals may be used for emphasis.

b) Paper

The quality of insert paper should be taken into consideration in order to ensure proper readability of the insert. The following should be considered:

i. The paper weight should be such that the paper is sufficiently thick to reduce transparency which makes reading difficult, particularly where the text size is small.

ii. Uncoated paper is preferred as glossy paper reflects light thus making information difficult to read.

iii. When the leaflet is folded the creases should not interfere with the readability of the information or lead to tearing of the insert.

1.2. Conformity with the Summary of Product Characteristics

The package insert should be in conformity with the summary of products characteristics.

1.3. Language

The labelling must be presented at least in English. An active style of writing should be used instead of passive.

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.

<text> signifies text to be selected or deleted as appropriate while {text} refers to information to be added.

PATIENT INFORMATION LEAFLET: INFORMATION FOR THE USER

{(Invented) name strength pharmaceutical form}

{Active pharmaceutical ingredient(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 health care provider.
- 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 becomes serious, or if you notice any side effects not listed in this leaflet, please tell your health care provider.

In this leaflet:

a. What {PRODUCT NAME} is and what it is used for
b. Before you <take> <use> {PRODUCT NAME}
c. How to <take> <use> {PRODUCT NAME}
d. Possible side effects
e. How to store {PRODUCT NAME}
f. Further information

i. WHAT {PRODUCT NAME} IS AND WHAT IT IS USED FOR

ii. 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 health care provider 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 health care provider 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}

iii. HOW TO <TAKE> <USE> {PRODUCT NAME}

<Always <take> <use> {PRODUCT NAME} exactly as your health care provider has told you. You should check with your health care provider 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 health care provider.>

iv. 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 health care provider.

v. 5. 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.>

vi. FURTHER INFORMATION

What {PRODUCT NAME} contains:

- The active pharmaceutical ingredient(s) is (are)…
- The other ingredient(s) is (are)...

What {PRODUCT NAME} looks like and contents of the pack:

Supplier and Manufacturer

{Name and address}

<{tel}>

<{fax}>

<{email}>

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

{Country}

{Name}

<{Address}

XXXX {City}>

Tel: + {telephone number}

<{preferably functional, i.e. not personalized, email}>

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

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

APPENDIX 6: FORMAT FOR DECLARATION BY EXPERT

I, the undersigned, declare that I have:

1. The suitable technical or professional qualifications to act in this capacity (for more information, refer to the enclosed curriculum vitae).
2. 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.
3. Provided a report based on my independent assessment of the data provided.
4. 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.

APPENDIX 7: FORMAT FOR LETTERS OF ACCESS TO APIMF AND CEP

ACTIVE PHARMACEUTICAL INGREDIENT MASTER FILE

The Secretary to the Authority, National Drug Authority
P. O. Box 23096 Kampala
Uganda

Dear Sir/Madam

Authorisation to access Active Pharmaceutical Ingredient Master File (APIMF)

Consent is hereby granted to National Drug Authority (NDA) to make reference to {APIMF holder's name}'s APIMF for {API name} in the evaluation of applications relating to {FPP name(s)} submitted to NDA by {applicant's name}.

This consent does/does not include authorisation 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 NDA APIMF procedure has been supplied to the applicant of the FPP.

A formal agreement exists between the applicant of the FPP and the manufacturer of the API which ensures that information will be communicated between them and to NDA before any significant change is made to the site of manufacture, manufacturing procedure or quality control specifications of the API. Except as permitted by NDA's Guidelines on Variations to Registered Pharmaceutical Products for Human Use, such changes will not be made to the API to be used in manufacture of the FPP destined to be distributed in Uganda before written approval is granted by NDA.

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

Any questions arising from NDA's evaluation of this APIMF should be forwarded to:

{Name and address}

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

CERTIFICATE OF SUITABILITY TO THE MONOGRAPHS OF THE EUROPEAN PHARMACOPOEIA

The Secretary to the Authority, National Drug Authority
P. O. Box 23096 Kampala
Uganda

Dear Sir/Madam

Authorisation to access the Certificate of Suitability to the Monographs of the European Pharmacopoeia (CEP)

Consent is hereby granted to National Drug Authority (NDA) to make reference to CEP No. {Certificate number and version} issued by the European Directorate for the Quality of Medicines (EDQM) on {date of issue} for {CEP holder's name}'s {drug substance name} in the evaluation of applications and relating to the registration of {FPP name(s)} submitted to NDA by the applicant {applicant's name}.

The substance is manufactured by:

{Names and addresses of all manufacturing sites, and manufacturing steps carried out at site}

Assurance is given that any conditions or additional testing requirements attached to the Certificate by the EDQM will be complied with for any batch of the API to be used in manufacture of FPPs to be distributed in Uganda.

A formal agreement exists between the applicant of the FPP and the manufacturer of the API which ensures that information will be communicated between them and to NDA before any significant change is made to the site of manufacture, manufacturing procedure or quality control specifications of the API. Except as permitted by NDA's Guidelines on Variations to Registered Pharmaceutical Products for Human Use, such changes will not be made to API to be used in manufacture of FPPs destined to be distributed in Uganda before written approval is granted by NDA.

Where relevant, any revised Certificates for this API will be forwarded to NDA for its information and records.

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 FPPs containing this material in Uganda.

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

{Name and address}

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

APPENDIX 8: QUALITY OVERALL SUMMARY - PRODUCT DOSSIER (QOS-PD)

Summary of product information:

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

2.3.S DRUG SUBSTANCE (or 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:		
a)	Certificate of suitability to the European Pharmacopoeia (CEP): Is a written commitment provided that the applicant will inform NDA 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:o 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 NDA; 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.	
b)	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.	
c)	Full details in the PD: • Summaries of the full information should be provided under the appropriate sections.	

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

2.3.S.1.1 Nomenclature (name, manufacturer)

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 (name, manufacturer)

a) Structural formula, including relative and absolute stereochemistry:
b) Molecular formula:

c) Relative molecular mass:

2.3.S.1.3 General Properties (name, manufacturer)

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

b) Solubilities:

c) In common solvents:

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

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

Dose/solubility volume calculation:

a) Physical form (e.g. polymorphic form(s), solvate, hydrate):
b) Polymorphic form:
c) Solvate:
d) Hydrate:
e) 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 (name, manufacturer)

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

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

Name and address (including block(s) / unit(s))	Responsibility	APIMF/CEP number (if 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 (name, manufacturer)

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 (name, manufacturer)

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

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

b) 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 (name, manufacturer)

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

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

2.3.S.2.5 Process Validation and/or Evaluation (name, manufacturer)

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

2.3.S.2.6 Manufacturing Process Development (name, manufacturer)

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 (name, manufacturer)

2.3.S.3.1 Elucidation of Structure and other Characteristics (name, manufacturer)

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 (name, manufacturer)

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

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

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

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

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

b) Basis for setting the acceptance criteria for impurities:

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

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

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

		Results (include batch number[4] and use[5])

[4] include strength, if reporting impurity levels found in the FPP (e.g. for comparative 2 studies)

[5]

Impurity (API-related and process-	**Acceptance Criteria**			

iii. ** e.g. comparative bioavailability or bio-waiver studies, stability (i) Justification of proposed acceptance criteria for impurities:

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

2.3.S.4.1 Specification (name, manufacturer)

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 (name, manufacturer)

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

2.3.S.4.3 Validation of Analytical Procedures (name, manufacturer)

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 (name, manufacturer)

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 (name, manufacturer)

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 (name, manufacturer)

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 (name, manufacturer)

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 (name, manufacturer)

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

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

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

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

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

Test	Results
Description	

Moisture	
Impurities	
Assay	
etc.	

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

2.3.S.7.2 Post-approval Stability Protocol and Stability Commitment (name, manufacturer)

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

2.3.S.7.3 Stability Data (name, manufacturer)

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 DRUG PRODUCT (or FINISHED PHARMACEUTICAL PRODUCT (FPP))

2.3.P.1 Description and Composition of the FPP

a) Description of the FPP:

b) Composition of the FPP:

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

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

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

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

f) 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:

b) 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:

c) 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	Relevant batches

and quality standard (e.g. NF, BP, Ph.Eur, inhouse)	Comparative bioavailability or biowaiver		Stability		Process validation		Commercial (2.3.P.1)	
	<Batch nos. and sizes>		<Batch nos. and sizes>		<Batch nos. and sizes>		<Batch nos. and sizes>	
	Theor. quantity per batch	%	Theor. quantity per batch	%	Theor. quantity per batch	%	Theor. quantity per batch	%

<complete with appropriate title e.g. Core tablet, Contents of capsule, Powder for injection>

Subtotal 1

<complete with appropriate title e.g. Film-coating >

Subtotal 2 Total

a) 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):

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

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

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

2.3.P. 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 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)

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.P4.4 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.P4.5 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 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

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):

b) 2.3.P.5.4 Batch Analyses

c) Description of the batches:

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

a) 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.				

b) 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	
	Qualification	
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 Specifications)

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

2.3.P.6 Reference Standards or Materials

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

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

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

2.3.P.7 Container Closure System

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

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

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

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

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

2.3.P.8 Stability

2.3.P.8.1 Stability Summary and Conclusions

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

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

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

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

Test	Results
Description	
Moisture	
Impurities	
Assay	
etc.	

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

Container closure system	Storage statement	Shelf-life

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

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

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

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

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

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

Parameter	Details	
Storage condition(s) (°C, % RH)		
Batch size(s), annual allocation	***<at least one production batch per year (unless none is produced that year) in each container***	
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.

APPENDIX 9: PRESENTATION OF BIOEQUIVALENCE TRIAL INFORMATION

BIOEQUIVALENCE TRIAL INFORMATION

General Instructions:

Please review all the instructions thoroughly and carefully prior to completing the Bioequivalence Trial Information Form (BTIF). Neither the format nor the content of the document (text and tables) should be changed, except for setting horizontal page layout in subsections including wide tables.

Provide as much detailed, accurate and final information as possible. Note that the greyed areas are NOT to be completed in by the applicant but are for NDA 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. Please ensure that the electronic submission has the same file structure and naming as the one employed to state the location of the documents and to include annexes of the BTIF as separate files.

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 the National Drug Authority (NDA)

A properly filled out and signed original copy of the BTIF with all its annexes (including a copy on CD-ROM) must be submitted to the NDA together with the bioequivalence part of the dossier.

BIOEQUIVALENCE TRIAL INFORMATION

1. SUMMARY

1.1. Summary of bioequivalence studies performed

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

1.2. Tabulation of the composition of the formulation(s) proposed for marketing and those used for bioequivalence studies

(State the location of the master formulae in the quality part of the submission) (Tabulate the composition of the biobatch 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.)

Composition of the batches used for bioequivalence studies					
Batch number					
Batch size (number of unit doses)1[6]					
Comments, if any					
Comparison of unit dose compositions and of clinical FPP batches (duplicate this table for each strength, if compositions are different)					
Ingredients (and quality standard)	**Function**	**Unit dose (mg)**	**Unit dose (%)**	**Biobatch (kg)**	**Biobatch (%)**
Total					
Equivalence of the compositions or justified					
Maximum intended commercial batch size					

2. CLINICAL STUDY REPORT

a) Study number:

b) Study title:

c) Location of study protocol:

[6] 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.

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

e) Dates of product administration:

2.1. ETHICS

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

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

2.2. 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)

2.3. STUDY OBJECTIVES

Briefly state the study objectives.

2.4. INVESTIGATIONAL PLAN

2.4.1. Overall study design and plan — description

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

2.4.2. Selection of study population

2.4.2.1. Inclusion Criteria

(List the inclusion criteria applied to subjects)

2.4.2.2. Exclusion Criteria

(List the exclusion criteria applied to subjects)

2.4.2.3. Health Verification

(State location of the individual data included in the submission)

a) List criteria used and all tests performed in order to judge health status

b) Indicate when tests were performed

c) Study site normal values

(State location in submission of study site normal values for blood clinical chemistry, haematology, and urinalysis clinical screen)

d) Report any results that were outside of study site normal values (State location in submission of the summary of anomalous values)

2.4.2.4. Removal of Trial subjects from Trial or assessment

a) Number of subjects enrolled in the study

(All subjects including alternates, withdrawals, and dropouts)

b) Alternates

(Please note: Generally, all subjects enrolled in the study should be included in the data set i.e., alternate subjects are strongly discouraged. However, in cases where there are alternate subjects, describe the procedure of including/excluding the alternates and whether alternates have been included in the study)

c) Withdrawals/dropouts

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

2.4.3. Products Administered

2.4.3.1. Test Product

a) Batch number, size, date of manufacture and expiry date for the test product

b) Potency (measured content) of test product as a percentage of label claim as per validated assay method

(This information should be cross-referenced to the location of the certificate of analysis in the submission)

2.4.3.2. Comparator (Reference) Product

(Append to this template a copy of product labelling (snap shot of the box, on which the name of the product, name and address of the manufacturer, batch number, and expiry date are clearly visible on the labelling)

a) Name and manufacturer of the comparator product and market where the comparator product was purchased

b) Batch number and expiry date for the comparator product

c) Purchase, shipment, storage of the comparator product

(Indicate from which company/pharmaceutical distributor the comparator product has been obtained. Clearly indicate in chronological order the steps and dates of shipment/transport from company of purchase to the study site. In addition, the storage conditions should be given. This information should be cross-referenced to location in submission of documents (e.g. receipts) proving conditions)

d) Potency (measured content) of the comparator product as a percentage of label claim, as measured by the same laboratory and under the same conditions as the test product

(This information should be cross-referenced to the location of the certificate of analysis in the submission)

e) Justification of choice of comparator product

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

2.4.4. 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)

2.4.5. 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

2.4.6. Blinding

2.4.6.1. 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:

2.4.6.2. Identify who held the study code and when the code was broken

2.4.7. Drug Concentration Measurements

2.4.7.1. Biological fluid(s) sampled

2.4.7.2. 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)

2.4.7.3. Sample Handling

a) Describe the method of sample collection

b) Describe sample handling and storage procedures

2.5. COMMENTS FROM REVIEW OF SECTION 2 – NDA USE ONLY

3. TRIAL SUBJECTS

3.1. 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

3.2. Subjects who smoke

a) Number of smokers included in the study

b) Indicate how many cigarettes smoked per day per subject

c) Comment on the impact on study

3.3. COMMENTS FROM REVIEW OF SECTION 3 – NDA USE ONLY

4. PROTOCOL DEVIATIONS

4.1. Protocol deviations during the clinical study

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

4.2. COMMENTS FROM REVIEW OF SECTION 4 – NDA USE ONLY

5. SAFETY EVALUATION

5.1. 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.)

5.2. COMMENTS FROM REVIEW OF SECTION 5 – NDA USE ONLY

6. EFFICACY EVALUATION

Efficacy results and tabulations of individual trial subjects' data

6.1. 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

6.2. Pharmacokinetic (PK) parameters

a) State how the pharmacokinetic parameters where calculated/obtained for AUC_{0-inf}, AUC_{0-t}, C_{max}, t_{max}, the elimination rate constant, and $t_{½}$ (indicate location of description in protocol)

b) State whether actual sampling time points were used for estimation of the pharmacokinetic parameters

c) Complete the table below

Test		**Reference**

Parameter	Arithmetic mean	Standard deviation	Inter-individual coefficient of variation (%)	Arithmetic mean	Standard deviation	Inter-individual coefficient of variation (%)
AUC_{0-t} (units)						
AUC_{0-inf} (units)						
C_{max} (units)						
t_{max} (units)						
$t_{½}$ (units)						

d) Ratio of AUC_{0-t} to AUC_{0-inf}

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

6.3. Statistical analysis

(State the method of calculation of the 90% confidence intervals for the ratio of test formulation over the reference formulation and indicate how treatment, period, sequence and subjects within sequence were included as factors in the ANOVA. Provide the following results from the ANOVA (parametric) on the logarithmically transformed AUC_{0-T} and C_{MAX} and

other relevant parameters. State software used for computing ANOVA.)

a) Geometric means, results from ANOVA, Degrees of Freedom (DF) and derived CV (intra-subject)

Parameter	**Test**	**Reference**	**% Ratio of geometric means**	**90 % Confidence interval**	**DF**	**CV (%)**
AUC_{0-t} (units)						
AUC_{0-inf} (units)						
C_{max} (units)						

b) Comparison of the results

(Compare the results, including mean values, inter- and intra-individual variability, of this study with published results (literature, product information of reference product

(innovator), WHOPARs), and copies of the references used should be appended to this document)

6.4. Discussion of results

(State location of the discussion of the results in the submission)

6.5. COMMENTS FROM REVIEW OF SECTION 6 – NDA USE ONLY

7. ANALYTICAL VALIDATION REPORT

7.1. Analytical technique

7.1.1. Validation protocol

(State the location of the validation protocol)

7.1.2. Identify analyte(s) monitored

7.1.3. Comment on source and validity of reference standard

7.1.4. Identify internal standard

7.1.5. Comment on source and validity of internal standard

7.1.6. Identify method of extraction

7.1.7. Identify analytical technique or method of separation employed

7.1.8. Identify method of detection

7.1.9. Identify anticoagulant used (if applicable)

7.1.10. If based on a published procedure, state reference citation

7.1.11. Identify any deviations from protocol

7.2. Selectivity

(Address the methods to verify selectivity against endogenous/exogenous compounds & results)

7.3. Sensitivity

(Address the methods to verify sensitivity & results)

7.4. Carry-over

(Summarize the method to verify carry-over & results)

7.5. Standard curves

(State location in submission of tabulated raw data and back calculated data with descriptive statistics)

a) List number and concentration of calibration standards used

b) Describe the regression model used including any weighting

c) List the back-calculated concentrations of the calibration standards of the validation runs (highlight the values outside of the acceptance range, e.g., 15%, except 20% for LLOQ)

7.6. Quality control samples

a) Identify the concentrations of the QC samples and the storage conditions employed prior to their analysis

7.7. Precision and accuracy during validation

a) Summarize inter-day/inter-run accuracy and precision of the calibration standards during assay validation

b) Summarize inter-day/inter-run accuracy and precision of the calibration standards during assay re-validation (If applicable)

c) Summarize inter-day/inter-run and intra-day/intra-run accuracy and precision of the QC samples during assay validation

d) Summarize inter-day/inter-run and intra-day/intra-run accuracy and precision of the QC samples during assay re-validation (If applicable)

7.8. Dilution integrity

(Summarize the method to verify dilution integrity & results)

7.9. Matrix effect (in case of MS detection)

(Summarize methods to verify the matrix effect & results)

7.10. Stability

(For each section provide the location of the raw data, a description of the methodology employed and a summary of the data.)

a) Summarize data on long-term storage stability

b) Summarize data on freeze-thaw stability

c) Summarize data on bench top stability

d) Summarize data on auto-sampler storage stability

e) Summarize data from any other stability studies conducted (e.g. long-term stock solution and working solution stability, short-term stock solution and working solution stability, dry-extract stability, wet-extract stability, stability in blood before sample processing)

7.11. Re-injection reproducibility

(Summarize the method to verify re-injection reproducibility & results)

7.12. COMMENTS FROM REVIEW OF SECTION 7 – NDA USE ONLY

8. BIOANALYTICAL STUDY REPORT

(State the location of the bioanalytical report for the analysis of the study subject samples)

8.1. Analytical technique

(Confirm whether the method is the same as the validated method and whether the same equipment was employed. Identify any differences between the validated method described above in Section 7 and the method employed for subject sample analyses)

8.1.1. Analytical protocol

(State the location of the analytical protocol)

8.1.2. Identify any deviations from protocol

8.1.3. Dates of subject sample analysis

8.1.4. Longest period of subject sample storage

(Identify the time elapsed between the first day of sample collection and the last day of subject sample analysis)

8.1.5. 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 (valid and failed runs, including reasons of failure).

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

d) List the back-calculated concentrations of the calibration standards of the study runs (highlight the values outside of the acceptance range, e.g., 15%, except 20% for LLOQ)

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

c) List the back-calculated concentrations of the QC samples of the study runs (highlight the values outside of the acceptance range, e.g., 15%)

d) Discuss whether the concentrations of the QC sample concentrations are similar to the concentrations observed in the study samples

e) State the percentage of QC samples per run with respect to the total number samples assayed in each run

8.4. Precision and accuracy

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

8.5. Repeat analysis (re-analysis, re-injection and re-integration)

a) List re-analysed samples by sample identification and include the following information for each re-analysis: initial value; reason for re-analysis; re-analysed value(s); accepted value; and reason for acceptance

b) Report the number of re-analysis as a percentage of the total number samples assayed

c) List re-injected samples by sample identification and include the following information for each re-injection: initial value; reason for re-injection; re-injected value; accepted value; and reason for acceptance

d) Report the number of re-injections as a percentage of the total number samples assayed

e) List re-integrated chromatograms by sample identification and include the following information for each re-integration: initial value; reason for re-integration; re-integrated value(s); accepted value; and reason for acceptance

f) Report the number of re-integrated chromatograms as a percentage of the total number of samples assayed

8.6. Incurred sample reanalysis

(State location in the submission and summarize the results of incurred sample reanalysis, including the number of subject samples included in ISR and the total number of samples analysed in the study)

8.7. Chromatograms

(State the location in the submission where the sample chromatograms can be found. The chromatograms should be obtained from a minimum of two analytical batches and include at least 20% of the subjects, up to a maximum of five. A complete set includes standards, QC samples, pre-dose and post-dose subject samples for both phases. Each chromatogram should be clearly labelled with respect to the following: date of analysis; subject ID number; study period; sampling time; analyte; standard or QC, with concentration; analyte and internal standard peaks; peak heights and/or areas)

8.8. COMMENTS FROM REVIEW OF SECTION 8 – NDA USE ONLY

9. QUALITY ASSURANCE

9.1. 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.)

9.2. Monitoring, auditing, inspections

(Provide a list of all monitoring and auditing reports of the study, and of recent inspections of study sites by regulatory agencies. State locations in the submission of the respective reports for each study site (see 3.2 b-d.)

9.3. COMMENTS FROM REVIEW OF SECTION 9 – NDA USE ONLY

10. CONCLUSIONS AND RECOMMENDATIONS – NDA USE ONLY

APPENDIX 10: GUIDELINES ON STABILITY TESTING OF ACTIVE PHARMACEUTICAL INGREDIENTS AND FINISHED PHARMACEUTICAL PRODUCTS

1. INTRODUCTION

1.1. Objectives of these guidelines

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

It is recommended that these guidelines 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 of these guidelines

These guidelines apply to new and existing APIs and address information to be submitted in original and subsequent applications for registration of their related FPP for human use. These guidelines are 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. GUIDELINES

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 (Appendix 1).

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:

a) when available, it is acceptable to provide the relevant data published

b) in the scientific literature to support the identified degradation products and pathways;

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

APIs intended for storage below -20 °C should be treated on a case-by-case basis. To establish the retest period, data should be provided on not less than three batches of at least pilot scale. The batches should be manufactured by the same synthesis route as production batches and using a method of manufacture and a procedure that simulates the final process to be used for production batches.

2.1.7.1. General case

Study storage condition minimum time period covered by data at submission:

Long-term: 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH

12 months or 6 months as described in point 2.1.7

Accelerated 40 °C ± 2 °C/75% RH ± 5% RH 6 months

2.1.7.2. Active pharmaceutical ingredients intended for storage in a refrigerator study storage condition Minimum time period covered by data at submission:

Long-term: 5°C ± 3 °C 12 months

Accelerated: 25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH

6 months: Whether accelerated stability studies are performed at 25 ± 2 °C/60% RH ± 5% RH or 30°C ± 2 °C/65% RH ±5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is based on a risk-based evaluation.

Testing at a more severe long term condition can be an alternative to storage testing at 25 °C/60% RH or 30 °C/65%RH. Data on refrigerated storage should be assessed according to the evaluation section of these guidelines, 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:

a) 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.

b) 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.

c) If the submission does not include stability data on production batches, a commitment should be made to place the first two or three production

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

d) 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 fi t 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:

a) number of batch(es) and different batch sizes, if applicable;

b) relevant physical, chemical, microbiological and biological test methods;

c) acceptance criteria;

d) reference to test methods;

e) description of the container closure system(s);

f) testing frequency;

g) 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

h) 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 pharmaceutical 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/65% RH ± 5% RH or
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:

a) 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.)

b) Any degradation product exceeding its acceptance criterion.

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

d) Failure to meet the acceptance criterion for pH; or

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

2.2.6.6. FPPs intended for storage below -20 °C

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

2.2.7. Stability commitment

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

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

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

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

c) If the submission does not include stability data on production batches, a commitment

d) should be made to place the first two or three production batches (see section 2.2.2) on long-term stability studies throughout the proposed shelf-life and on accelerated studies for six months.

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

2.2.8. Evaluation

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

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

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

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

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

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

d) The manufacturer will continue to conduct long-term studies until the proposed shelf- life has been covered, and the results obtained will be submitted to National Drug 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:

a) change in the manufacturing process;

b) change in the composition of the FPP;

c) change of the immediate packaging;

d) 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 registration has been granted, the stability of the FPP should be monitored according to a continuous appropriate programme that will permit the detection of any stability issue (e.g. changes in levels of impurities or dissolution profile) associated with the formulation in the container closure system in which it is marketed.

The purpose of the On- going stability programme is to monitor the product over its shelf-life and to determine that the product remains, and can be expected to remain, within specifications under the storage conditions on the label.

This mainly applies to the FPP in the container closure system in which it is supplied, but consideration should also be given to inclusion in the programme of bulk products. For example, when the bulk product is stored for a long period before being packaged and/ or shipped from a manufacturing site to a packaging site, the impact on the stability of the packaged product should be evaluated and studied.

Generally, this would form part of development studies, but where this need has not been foreseen, inclusion of a one- off study in the on-going stability programme could provide the necessary data. Similar considerations could apply to intermediates that are stored and used over prolonged periods.

The on-going stability programme should be described in a written protocol and results formalized as a report.

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

a) number of batch(es) per strength and different batch sizes, if applicable. The batch size should be recorded, if different batch sizes are employed;

b) relevant physical, chemical, microbiological and biological test methods;

c) acceptance criteria;

d) reference to test methods;

e) description of the container closure system(s);

f) testing frequency;

g) 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

h) 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 registration 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 these guidelines. 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.

The Quality Assurance of Medicines Terminology Database was established in August 2005 and includes the definitions of terms related to quality assurance of medicines.

This database is intended to help harmonize terminology and to avoid misunderstandings that may result from the different terms and their interpretations used in various WHO publications. The main publications used as a source of

information to create the Quality Assurance of Medicines Terminology Database are the quality assurance guidelines included in the 36th-42nd reports of the WHO Expert Committee on Specifications for Pharmaceutical Preparations.

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 a 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 confi m the projected re-test period and shelf-life, and to recommend storage conditions.

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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 longterm data for the FPP to be marketed in the proposed container closure system.

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

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

significant change
(See section 2.2.6.1.)
In general “significant change” for an FPP is defined as:

a) A 5% or more change in assay from its initial content of API(s), or failure to meet the acceptance criteria for potency when using biological or immunological procedures. (Note: other values may be applied, if justified, to certain products, such as multivitamins and herbal preparations.)
b) Any degradation product exceeding its acceptance criterion.
c) Failure to meet the acceptance criteria for appearance, physical attributes and functionality test (e.g. colour, phase separation, resuspendability, caking, hardness, dose delivery per actuation). However, some changes in physical attributes (e.g. softening of suppositories, melting of creams or partial loss of adhesion for transdermal products) may be expected under accelerated conditions. Also, as appropriate for the dosage form:
d) Failure to meet the acceptance criterion for pH. or
e) Failure to meet the acceptance criteria for dissolution for 12 dosage units.

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

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

stress testing (of the API)
Studies undertaken to elucidate the intrinsic stability of API. 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 photostability 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 multidose container can be used.

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a) Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report. Geneva, World Health Organization, 1996, Annex 5 (WHO Technical Report Series, No. 863).

b) Regional Guidelines on stability testing of active substances and pharmaceutical products for the WHO Eastern Mediterranean Region. August 2006 (http://www.emro.who.int/edb/media/pdf/EMRC5312En.pdf).

c) The following ICH Guidelines may be consulted in the context of stability testing:

i. International Conference on Harmonisation. ICH Q1A (R2): Stability testing of new drug substances and products (http://www.ich.org/LOB/media/ MEDIA419. pdf).

ii. International Conference on Harmonisation. ICH Q1B: Photostability testing of new drug substances and products (http://www.ich.org/LOB/media/MEDIA412. pdf).

ii. International Conference on Harmonisation. ICH QIC: Stability testing of new dosage forms (http://www.ich.org/LOB/media/MEDIA413.pdf).

iii. International Conference on Harmonisation. ICH Q1D: Bracketing and matrixing designs for stability testing of new drug substances and products (http://www. ich.org/LOB/media/MEDIA414.pdf).

iv. e) International Conference on Harmonisation. ICH Q1E: Evaluation for stability data (http://www.ich.org/LOB/media/MEDIA415.pdf).

v. International Conference on Harmonisation. ICH Q2R1): Validation of analytical procedures: text and methodology (http://www.ich.org/LOB/media/MEDIA417. pdf).

vi. International Conference on Harmonisation. ICH Q3A: Impurities in new drug substances (http://www.ich.org/LOB/media/MEDIA422.pdf).

vii. International Conference on Harmonisation. ICH Q3B: Impurities in new drug products (http://www.ich.org/LOB/media/MEDIA421.pdf).

viii. International Conference on Harmonisation. ICH Q5C: Stability testing of biotechnological/biological products (http://www.ich.org/LOB/media/ MEDIA427. pdf).

ix. International Conference on Harmonisation. ICH Q6A: Specifi cations: Test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances (http://www.ich.org/LOB/media/MEDIA430. pdf).

x. International Conference on Harmonisation. ICH Q6B: Specifi cations: Test procedures and acceptance criteria for biotechnological/biological products (http://www.ich.org/LOB/media/MEDIA432.pdf).

xi. Further information can be found on the ICH homepage: http://www.ich.org/cache/compo/276-254-1.html.

d) Guidelines on active pharmaceutical ingredient master file procedure. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-second report. Geneva, World Health Organization, 2008, Annex 4 (WHO Technical Report Series, No. 948).

e) WHO guidelines for stability evaluation of vaccines. In: WHO Expert Committee on Biological Standardization. Fifty-seventh report. Geneva, World Health Organization (WHO Technical Report Series, (in press)) (http://www.who.int/biologicals/publications/trs/areas/vaccines/stability/en/index.html).

f) Schumacher P 1972. Uber eine fur die Haltbarkeit von Arzneimitteln ma&gebliche Klimaeinteilung [The impact of climate classifi cation on the stability of medicines]. Die Pharmazeutische Industrie, 34:481-483.

g) Grimm W. 1986. Storage conditions for stability testing (Part 2). Drugs Made in Germany, 29:39-47.

h) Grimm W. 1998. Extension of the International Conference on Harmonisation Tripartite Guidelines for stability testing of new drug substances and products to countries of Climatic Zones III and IV. Drug Development and Industrial Pharmacy, 24:313-325.

i) Zahn M. et al. 2006. A risk-based approach to establish stability testing conditions for tropical countries. Journal of Pharmaceutical Sciences, 95:946-965. Erratum: Journal of Pharmaceutical Sciences, 2007, 96:2177.

j) Guidelines for registration of fixed-dose combination pharmaceutical products. Appendix 3: Pharmaceutical development (or preformulation) 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).

k) Supplementary guidelines on good manufacturing practices: validation. In: Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2, 2nd updated edition. Good manufacturing practices and inspection. Geneva, World Health Organization, 2007, Chapter 1.

l) WHO good manufacturing practices: main principles for pharmaceutical products. In: Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2, 2nd updated edition. Good manufacturing practices and inspection. Geneva, World Health Organization, 2007, Chapter 1.

m) Guidance on variations to a prequalified product dossier. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first report. Geneva, World Health Organization, 2007, Annex 6 (WHO Technical Report Series, No. 943). Prequalification Programme - Priority Essential Medicines. A

United Nations Programme managed by WHO. Information for applicants (http://mednet3.who.int/ prequal/).

n) 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 pharmaceutical 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 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 pharmaceutical 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
a) Hard gelatin capsules: brittleness, dissolution (or disintegration, if justified), water content and level of microbial contamination.
b) 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 optic preparations

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

a) 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).

b) 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.

c) Evaluation of cutaneous sprays should include: pressure, weight loss, net weight dispensed, delivery rate, level of microbial contamination, spray pattern, 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.

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

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

c) Large volume parenterals (LVPs)

d) 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.

Recommended labelling statements for active pharmaceutical ingredients (APIs)

Table 1

Testing condition under which the stability of the API has been	Recommended labelling statement
30ºC/65% RH (long-term) 400C/75% RH (accelerated)	"Do not store above 30ºC" *
30ºC/75% RH (long-term) 400C/75% RH (accelerated)	"Do not store above 30ºC"
5ºC ± 3 °C	''Store in a refrigerator (2ºC to 8ºC)"
-20ºC ± 5ºC	"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.

Recommended labelling statements for finished pharmaceutical products (FPPs)

Table 2

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

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

APPENDIX 11: PRODUCT QUALITY REVIEW 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.

APPENDIX 12: GUIDELINES ON THERAPEUTIC EQUIVALENCE REQUIREMENTS

ABBREVIATIONS AND ACRONYMS

$AUC_{(0-\sim)}$	:	Cumulative urinary excretion of unchanged drug from administration until time t;
$AUC_{(O-T)}$	:	Area under the plasma concentration curve from administration to last observed concentration at time t;
$AUC_{(0-72h)}$	:	Area under the plasma concentration curve extrapolated to infinite time;
C_{max}	:	AUC during a dosage interval at steady state;
$C_{max,\ ss}$	:	Area under the plasma concentration curve from administration to 72h; Maximum plasma concentration;
residual area	:	Maximum plasma concentration at steady state;
R_{max}	:	Extrapolated area ($AUC_{(0-M)}$ - $AUC_{(0-t)}$)/ $AUC_{(0-M)}$
t_{max}	:	Maximal rate of urinary excretion;
$t_{max,ss}$	:	Time until C max is reached
$Ae_{(O-t)}$	:	Time until C is reached;
$AUC_{(O-t)}$	:	Plasma concentration half-life
$V_{1/2}$	:	Terminal rate constant
SmPC	:	Summary of Product Characteristics

DEFINITIONS

Pharmaceutical equivalence

Pharmaceutical products are pharmaceutically equivalent if they contain the same amount of the same active substance(s) in the same dosage forms that meet the same or comparable standards. Pharmaceutical equivalence does not necessarily imply bioequivalence as differences in the excipients and/or the manufacturing process can lead to faster or slower dissolution and/or absorption.

Pharmaceutical alternatives

Pharmaceutical alternatives are pharmaceutical products with different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active moiety, or which differ in dosage form or strength.

1. INTRODUCTION

The objective of this guideline is to specify the requirements for the design, conduct, and evaluation of bioequivalence studies for immediate release and modified release dosage forms with systemic action.

Two pharmaceutical 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}.

The purpose of establishing bioequivalence is to demonstrate equivalence in biopharmaceutics quality between the generic pharmaceutical product and a comparator pharmaceutical product in order to allow bridging of preclinical tests and of clinical trials associated with the comparator pharmaceutical product.

The definition for generic pharmaceutical products is a product that has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the comparator pharmaceutical product, and whose bioequivalence with the comparator pharmaceutical 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 hybrid 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 pharmaceutical product containing a new chemical entity and to comparative bioavailability studies included in extension or hybrid 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, section3.2.P.2 (Pharmaceutical Development).

SCOPE

This guideline focuses on recommendations for bioequivalence studies for immediate release formulations and modified release with systemic action. The scope is limited to chemical entities. Biological products are not covered by these guidelines.

In case bioequivalence cannot be demonstrated using drug concentrations, in exceptional circumstances pharmacodynamic or clinical endpoints may be needed.

2. 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 3.5, 3.6 and 3.7).

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 pharmaceutical product approved by National Drug Authority. 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 comparator products that are not approved by NDA should not be submitted and do not need to be included in the list of studies.

2.1 Study design

2.1.1 Standard design

If two formulations are compared, a randomised, two-period, two-sequence single dose crossover design is recommended. The treatment periods should be separated by a wash out period sufficient to ensure that drug concentrations are below the lower limit of bioanalytical quantification in all subjects at the beginning of the second period. Normally at least 5 elimination half-lives are necessary to achieve this. The study should be designed in such a way that the treatment effect (formulation effect) can be distinguished from other effects. In order to reduce variability a cross over design usually is the first choice.

2.1.2 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 3.10.9). The study should be designed in such a way that the formulation effect can be distinguished from other effects.

Other designs or methods may be chosen in specific situations, but should be fully justified in the protocol and final study report. The subjects should be allocated to treatment sequences in a randomised order. In general, single dose studies will suffice, but there are situations in which steady-state studies may be required:

a) If problems of sensitivity preclude sufficiently precise plasma concentration measurement after single dose;

b) If the intra-individual variability in the plasma concentrations or disposition rate is inherently large;

c) in the case of dose-or time-dependent pharmacokinetics;

d) in the case of extended release products (in addition to single dose studies)

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 3.7). 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).

2.2 Comparator and test product

2.2.1 Comparator pharmaceutical Products

Test products in an application for a generic or hybrid product or an extension of a generic/ hybrid product are normally compared with the corresponding dosage form of an innovator pharmaceutical product, if available on the market.

The product used as comparator product in the bioequivalence study should meet the requirements in the guidelines on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products available in: **WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty- sixth report. Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902)161- 180.**

In an application for extension of a pharmaceutical product which has been initially approved by NDA and when there are several dosage forms of this pharmaceutical product on the market, it is recommended that the dosage form used for the initial approval of the concerned pharmaceutical product (and which was used in clinical efficacy and safety studies) is used as comparator product, if available on the market.

2.2.2 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.

c) In case of a production batch smaller than 100,000 units, a full production batch will be required.

d) The characterisation and specification of critical quality attributes of the drug product, such as dissolution, should be established from the test batch, i.e. the clinical batch for which bioequivalence has been demonstrated.

e) 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.

f) Comparative dissolution profile testing should be undertaken on the first three production batches.

g) 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.

h) 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.

2.3 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.

2.4 Subjects

2.4.1 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. In general, the recommended number of 24 normal healthy subjects, preferably non-smoking. A number of subjects of less than 24 may be accepted (with a minimum of12 subjects) when statistically justifiable. However, in some cases (e.g. for highly variable drugs) more than 24 subjects are required for acceptable bioequivalence study. 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.

2.4.2 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 pharmaceutical 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 should be 1 between18-50years in age, preferably have a Body Mass Index between 18.5 and 30 kg/ m2 and within15% of ideal body weight, height and body build to be enrolled in a crossover bioequivalence study.

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.

2.4.3 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.

2.5 Study conduct

2.5.1 Standardisation of the bioequivalence studies

The test conditions should be standardised in order to minimise the variability of all factors involved except that of the products being tested. Therefore, it is recommended to standardise 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 standardised 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 standardised 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, (see section 3.5.4) the timing of administration of the drug 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 drug 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 standardised.

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.

Pharmaceutical 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).

2.5.2 Sampling and 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 $AUC_{(0-\sim)}$. 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 $AUC_{(0-\sim)}$). 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 72h for immediate release formulations. A sampling period longer than 72h 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 $AUC_{(0-T)}$.

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 3.6).

For endogenous substances, the sampling schedule should allow characterisation of the endogenous baseline profile for each subject in each period. Often, a baseline is determined from 2-3 samples taken before the drug 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 3.6).

2.5.3 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).

2.5.4 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 pharmaceutical 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 pharmaceutical 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 (%)).

2.6 Characteristics to be investigated

2.6.1 Pharmacokinetic parameters (Bioavailability Metrics)

Actual time of sampling should be used in the estimation of the pharmacokinetic parameters. In studies to determine bioequivalence after a single dose, $AUC_{(0-t)}$, $AUC_{(0-m)}$, residual area, C and t should be determined. In studies with a sampling period of 72h, and where the concentration at 72h is quantifiable, $AUC_{(0-\sim)}$ and residual area do not need to be reported; it is sufficient to report AUC truncated at 72h, $AUC_{(0-72h)}$. Additional parameters that may be reported include the terminal rate constant, A_z, and $t_{1/2}$

In studies to determine bioequivalence for immediate release formulations at steady state, $AUC_{(0-T)}$, $C_{max,ss,}$ and t_{max}, should be determined.

When using urinary data, $Ae_{(0-t)}$ and, if applicable, R_{max} should be determined.

Non-compartmental methods should be used for determination of pharmacokinetic parameters in bioequivalence studies. The use of compartmental methods for the estimation of parameters is not acceptable.

2.6.2 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.

2.6.3 Inactive pro-drugs

Also for inactive prodrugs, 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.

2.6.4 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.

2.6.5 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.

2.6.6 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 (AeJ 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.

2.6.7 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.

2.7 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.

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 3.11).

2.8 Linear and Non- Linear pharmacokinetics

2.8.1 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 drug substance is highly, 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.

2.8.2 Non-linear pharmacokinetics

For drugs with non-linear pharmacokinetics characterised 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 a 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.

2.8.3 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.

2.8.4 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.

2.9 Bioanalytical methodology

The bioanalysis of bioequivalence samples should be performed in accordance with the principles of Good Laboratory Practice (GLP)-OECD. However, as human bioanalytical studies fall outside the scope of GLP, the sites conducting the studies are not required to be monitored as part of a national GLP compliance programme.

The bioanalytical methods used to determine the active principle and/or its biotransformation products in plasma, serum, blood or urine or any other suitable matrix must be well characterised, fully validated and documented to yield reliable results that can be satisfactorily interpreted. Within study validation should be performed using Quality control samples in each analytical run.

The main objective of method validation is to demonstrate the reliability of a particular method for the quantitative determination of analyte(s) concentration in a specific biological matrix. The main characteristics of a bioanalytical method that is essential to ensure the acceptability of the performance and the reliability of analytical results includes but not limited to: selectivity, sensitivity, lower limit of quantitation, the response function (calibration curve performance), accuracy, precision and stability of the analyte(s) in the biological matrix under processing conditions and during the entire period of storage.

The lower limit of quantitation should be 1/20 of C_{max} or lower, as pre-dose concentrations should be detectable at 5% of C_{max} or lower (see section 9.0 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.
Bioanalytical method validation should be done according to the EMA Guideline on bioanalytical method validation, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500109686.pdf

The validation report of the bioanalytical method should be included in Module 5 of the application.

2.10 Evaluation of Bioequivalence studies

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 3.2 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.

2.10.1 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.

2.10.2 Reasons for exclusion

Unbiased assessment of results from randomised studies requires that all subjects are observed and treated according to the same rules. These rules should be independent from treatment or outcome. In consequence, the decision to exclude a subject from the statistical analysis must be made before bioanalysis.

In principle any reason for exclusion is valid provided it is specified in the protocol and the decision to exclude is made before bioanalysis. However the exclusion of data should be avoided, as the power of the study will be reduced and a minimum of 12 evaluable subjects is required.

Examples of reasons to exclude the results from a subject in a particular period are events such as vomiting and diarrhoea which could render the plasma concentrationtime profile unreliable. In exceptional cases, the use of concomitant medication could be a reason for excluding a subject.

The permitted reasons for exclusion must be pre-specified in the protocol. If one of these events occurs it should be noted in the CRF as the study is being conducted. Exclusion of subjects based on these pre-specified criteria should be clearly described and listed in the study report.

Exclusion of data cannot be accepted on the basis of statistical analysis or for pharmacokinetic reasons alone, because it is impossible to distinguish the formulation effects from other effects influencing the pharmacokinetics.

The exceptions to this are:

a) A subject with lack of any measurable concentrations or only very low plasma concentrations for comparator pharmaceutical product. A subject is considered to have very low plasma concentrations if its AUC is less than 5% of comparator pharmaceutical product geometric mean AUC (which should be calculated without inclusion of data from the outlying subject). The exclusion of data due to this reason will only be accepted in exceptional cases and may question the validity of the trial.

b) Subjects with non-zero baseline concentrations > 5% of C_{max}. Such data should be excluded from bioequivalence calculation (see carry-over effects below).

The above can, for immediate release formulations, be the result of subject non-compliance and an insufficient wash-out period, respectively, and should as far as possible be avoided by mouth check of subjects after intake of study medication to ensure the subjects have swallowed the study medication and by designing the study with a sufficient wash-out period. The samples from subjects excluded from the statistical analysis should still be assayed and the results listed (see Presentation of data below).

As stated in section 5.0; Study conduct, $AUC_{(0-t)}$ 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 $AUC_{(0-\infty)}$, 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 $AUC_{(0-t)}$

2.10.3 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 3.10.8). Moreover, for highly variable drug products the acceptance interval for C_{max} may in certain cases be widened (see section 3.10.9).

2.10.4 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 bioiequivalence 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.

2.10.5 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.

2.10.6 Two-stage design

It is acceptable to use a two-stage approach when attempting to demonstrate bioequivalence. An initial group of subjects can be treated and their data analysed.

If bioequivalence has not been demonstrated an additional group can be recruited and the results from both groups combined in a final analysis. If this approach is adopted appropriate steps must be taken to preserve the overall type I error of the experiment and the stopping criteria should be clearly defined prior to the study.

The analysis of the first stage data should be treated as an interim analysis and both analyses conducted at adjusted significance levels (with the confidence intervals accordingly using an adjusted coverage probability which will be higher than 90%). For example, using 94.12% confidence intervals for both the analysis of stage 1 and the combined data from stage 1 and stage 2 would be acceptable, but there are many acceptable alternatives and the choice of how much alpha to spend at the interim analysis is at the company's discretion. The plan to use a two-stage approach must be pre-specified in the protocol along with the adjusted significance levels to be used for each of the analyses.

When analysing the combined data from the two stages, a term for stage should be included in the ANOVA model.

2.10.7 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 randomisation 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.

2.10.8 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

2.10.9 Highly variable drugs or drug products

Highly variable drug products (HVDP) are those whose intra-subject variability for a parameter is larger than 30%. If an applicant suspects that a drug 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 is considered clinically irrelevant based max **J**

On a sound clinical justification can be assessed with a widened acceptance range. If this is the case the acceptance criteria for C can be widened to a maximum of 69.84 – max 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], 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

$\sqrt{*\ CV(\%)} = 100e^{sWR2} - 1$

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.

2.11 In vitro dissolution tests

General aspects of in vitro dissolution experiments are briefly outlined in (annex 1) including basic requirements how to use the similarity factor (f2-test).

2.11.1 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 drug 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.

2.11.2 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 section (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 pharmaceutical product should then confirm that this finding is drug substance 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). For details refer to NDA guidelines on biowaiver.

2.12 Reporting of bioequivalence study results

The report of a bioavailability or bioequivalence study should be summarized in the bioequivalence trial information (Appendix).

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 pharmaceutical product is in accordance with NDA's list of comparator products. This should include the comparator product name, strength, pharmaceutical form, batch number, manufacturer, expiry date and country of purchase.

The name and composition of the test product(s) used in the study should be provided. The batch size, batch number, manufacturing date and, if possible, the expiry date of the test product should be stated.

Certificates of analysis of comparator and test batches used in the study should be included in an appendix to the study report.

Concentrations and pharmacokinetic data and statistical analyses should be presented in the level of detail described above (section 9.7 Presentation of data).

2.13 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 authorisation. A confirmation whether the test product is already scaled-up for production should be submitted. Comparative dissolution profiles (see section 3.11; In vitro dissolution tests) should be provided.

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 randomisation 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.

3.0 OTHER APPROACHES TO ASSESS THERAPEUTIC EQUIVALENCE

3.1 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.

3.2 Comparative clinical studies

If a clinical study is considered as being undertaken to prove equivalence, the same statistical principles apply as for the bioequivalence studies. The number of patients to be included in the study will depend on the variability of the target parameters and the acceptance range, and is usually much higher than the number of subjects in bioequivalence studies.

3.3 Special considerations for modified - release drug products

For the purpose of these guidelines modified release products include:

a) Delayed release

b) Sustained release

c) Mixed immediate and sustained release

d) Mixed delayed and sustained release

Mixed immediate and delayed release Generally, these products should

a) Acts as modified -release formulations and meet the label claim

b) Preclude the possibility of any dose dumping effects

c) There must be a significant difference between the performance of modified release product and the conventional release product when used as reference product.

d) 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.

e) Produce consistent Pharmacokinetic performance between individual dosage units; and

f) Produce plasma levels which lie within the therapeutic range (where appropriate) for the proposed dosing intervals at steady state.

If all of the above conditions are not met but the applicant considers the formulation to be acceptable, justification to this effect should be provided.

a) Study Parameters

Bioavailability data should be obtained for all modified release drug 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 drug substances, and the extent of accumulation of the drug after repeated dosing.

If formulation is the first market entry of the APIs, the products pharmacokinetic parameters should be determined. If the formulation is a second or subsequent market entry then the comparative

bioavailability studies using an appropriate reference product should be performed

b) Study design

Study design will be single dose or single and multiple dose based on the modified release products that are likely to accumulate or unlikely to accumulate both in fasted and non- fasting state. If the effects of food on the reference product is not known (or it's known that food effects 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. It is known with certainty (e. g from published data) that the reference product is not affected by food, then a three-way cross - over study may be appropriate with.

i. The reference product in the fasting
ii. The test product in the fasted state, and
iii. The test product in the fed state.

c) Requirement for modified release formulations unlikely to accumulate.

This section outlines the requirements for modified release formulations which are used at a dose interval that is not likely to lead to accumulation in the body (AUC_{0-v} /AUC^ ≥ 0.8)
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 perfomed 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}, $AUC_{0-t,}$ $AUC_{0-"}$, Cmax (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 Reference) of the geometric mean AUC (for both AUC_{0-t} and AUC_{0-t}) and C_{max} (Where the comparison is with an existing modified release product) should generally be within the range 80 to 125% both in the fasting state and following the administration of an appropriate meal at a specified time before taking the drug.

The Pharmacokinetic parameters should support the claimed dose delivery attributes of the modified release - dosage form.

d) Requirement for modified release formulations likely to accumulate.

This section outlines the requirement for modified release formulations that are used at dose intervals that are likely to lead to accumulation (AUC /AUC c o.8)

When a modified release product is the first market entry of the modified release type, the reference formulation is normally the innovators immediate - release formulation. Both a single dose and steady state doses of the modified release formulation should be compared with doses of the immediate - release formulation which it is intended to replace. The immediate - release product should be administered according to the conventional dosing regimen.

Studies should be performed with single dose administration in the fasting state as well as following an appropriate meal. In addition, studies are required at steady state. The following pharmacokinetic parameters should be calculated from single dose studies; AUC_{0-t}, $AUC_{0-t,}$ $AUC_{0-"}$, 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} 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 formulations are compared at steady state.

90% confidence interval for the ration of geometric means (Test Reference drug) for AUC0-t, Cmax and Cmin determined using log - transformed data should generally be within the range 80 to 125% when the formulations 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 voluntees 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, pharmackodynamic studies in humans are required if measurement of drug concentrations cannot be used as surrogative 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 recognised when planning, conducting and assessing the results from a pharmacodynamic study;

a) The response measured should be a pharmacological or therapeutically effects which is relevant to the claims of efficacy and /or safety of the drug.

b) The methodology adopted for carrying out the study the study should be validated for precision, accuracy, reproducibility and specificity.

c) 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.

d) The response should be measured quantitatively under double - blind conditions and be recorded in a 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.

e) 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.

f) 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.

g) A crossover or parallel study design should be used, appropriate.

h) 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.

i) There should be knowledge of the reproducibility of the base - line conditions.

j) Statistical considerations for the assessments of the outcomes are in principle, the same as in Pharmacokinetic studies.

k) 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 to 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 drug products when pharmacokinetic and phamacodynamic 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 pharmaceutical 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:

   i. To get information on the test batches used in bioavailability/bioequivalence studies and pivotal clinical studies to support specifications for quality control

   ii. To be used as a tool in quality control to demonstrate consistency in manufacture

   iii. To get information on the reference product used in bioavailability/ bioequivalence studies and pivotal clinical studies.

b) Bioequivalence surrogate inference

   i. To demonstrate in certain cases similarity between different formulations of an active substance and the reference pharmaceutical product (biowaivers e.g., variations, formulation changes during development and generic pharmaceutical products; see section 4.2 and App. III)

   ii. 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 given in section 1 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 /2 statistic as follows:

$$f_2 = 50 \cdot \log\left[\frac{100}{\sqrt{1+\frac{\sum_{t=1}^{t=n}\left[\overline{R}(t)-\overline{T}(t)\right]^2}{n}}}\right]$$

In this equation /2 is the similarity factor, n is the number of time points, R(t) is the mean percent reference drug dissolved at time t after initiation of the study; T(t) is the mean percent test drug dissolved at time t after initiation of the study. For both the reference and test formulations, percent dissolution should be determined.

The evaluation of the similarity factor is based on the following conditions:

a) A minimum of three time points (zero excluded)

b) The time points should be the same for the two formulations

c) Twelve individual values for every time point for each formulation

d) Not more than one mean value of > 85% dissolved for any of the formulations.

e) 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 f_2 value between 50 and 100 suggests that the two dissolution profiles are similar.

When the /2 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 /2 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 pharmaceutical 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, in vivo bioequivalence studies may in some situations not be required.

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. For orodispersable tablets and oral solutions specific recommendations apply, as detailed below.

Orodispersible tablets:
An orodispersable 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. 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/hybrid to an approved ODT reference pharmaceutical product, the following recommendations regarding study design apply:

a) if the reference pharmaceutical product can be taken with or without water, bioequivalence should be demonstrated without water as this condition best resembles the intended use of the formulation. This is especially important if the substance may be dissolved and partly absorbed in the oral

cavity. If bioequivalence is demonstrated when taken without water, bioequivalence when taken with water can be assumed.

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

c) if the reference pharmaceutical 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.

APPENDIX 13: GUIDELINES FOR APPLICATION FOR BIOPHARMACEUTICS CLASSIFICATION SYSTEM BASED BIOWAIVERS

ABBREVIATIONS AND ACRONYMS

APIs	Active Pharmaceutical Ingredients
BCS	Biopharmaceutics Classification System
CoA	Certificate of Analysis
EMA	European Medical Association
f_2	Similarity Factor
ICH	International Conference on Harmonisation LTR - Local Technical Representative pKa - Dissociation constant SD - Standard deviation
USFDA	United States Food and Drug Administration

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 safety can be expected to be essentially the same. Bioequivalence focuses on the equivalence of release of the active pharmaceutical ingredient from the pharmaceutical product and its subsequent absorption into the systemic circulation. Comparative studies using clinical or pharmacodynamic end points may also be used to demonstrate bioequivalence.

Biopharmaceutics Classification System (BCS)-based biowaivers are meant to reduce the need for establishing ***in vivo*** bioequivalence in situations where ***in vitro*** data may be considered to provide a reasonable estimate of the relative ***in vivo*** performance of two products. The BCS is a scientific approach designed to predict pharmaceutical 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 multisource 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. The selection of the comparator product is provided in the guidelines for selection of comparator product.

Critical dose pharmaceutical product - Pharmaceutical product where comparatively small differences in dose or concentration lead to dose- and concentration-dependent, serious therapeutic failures and/or serious adverse pharmaceutical 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/millilitre (mg/mL)] at a given pH and temperature. For example, if a Pharmaceutcial 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 Uganda. If not currently approved in Uganda, 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.

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.

1.1 INTRODUCTION

The Biopharmaceutics Classification System (BCS)-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 the equivalence in the in vivo performance can be justified by satisfactory ***in vitro*** data. Provided certain prerequisites are fulfilled as outlined in this document comparative ***in vitro*** dissolution could be even more discriminative than ***in vivo*** studies.

Applying for a BCS-based biowaiver is restricted to highly soluble drug substances with known human absorption and considered non-critical in terms of therapeutic range. Hence, those drugs for which tighter acceptance ranges of 90 - 111 % would apply in ***in vivo*** bioequivalence studies are not eligible for the BCS-based biowaiver approach. Furthermore, the concept is applicable to pharmaceutically equivalent immediate release, solid pharmaceutical forms for oral administration and systemic action. However, it is not applicable for sublingual, buccal, orodispersible, and modified release formulations.
BCS-based biowaiver are intended only to address the question of bioequivalence between a test and a reference product. Hence, respective investigations may be useful to prove bioequivalence between early clinical trial products and to-be-marketed products, generics and innovator products, and in the case of variations that require bioequivalence testing.

Objectives

To provide applicants of new pharmaceutical submissions with the information necessary to comply with respect to BCS-based biowaivers for comparative bioavailability studies to be used in support of the safety and efficacy of a pharmaceutical product.

When an application for a BCS-based biowaiver of comparative bioavailability studies versus a comparator product is submitted in support of the safety and efficacy of a pharmaceutical, the relevant Pharmaceutical Product and pharmaceutical product characteristics should meet the standards described in these guidelines in order to ensure compliance with the Regulations.

In vivo human data collected for the purpose of submission to NDA should be collected in accordance with generally accepted clinical practices that are designed to ensure the protection of the rights, safety and well-being of subjects. They should be collected in compliance with the International Conference on Harmonisation (ICH) Guidelines (Topic E6) on Good Clinical Practice. The principles of Good Manufacturing Practice as indicated in NDA GMP guidelines should be adhered to wherever applicable.

Scope

The data requirements and acceptance criteria outlined in these guidelines are intended to be applied to all applications for a BCS-based biowaiver of comparative bioavailability studies which provide pivotal evidence of the safety and efficacy of a product. These guidelines are designed to facilitate applicants seeking to waive bioequivalence studies, based on the BCS. Examples of cases where these guidelines apply are:

a) Biowaivers for comparative bioavailability studies in support of the bioequivalence of subsequent-entry products;

b) Biowaivers for bridging studies where the formulation to be marketed is different from the formulation used in the pivotal clinical trials;

c) Biowaivers for studies in support of significant post-approval changes and product line extensions; and

d) Biowaivers for comparative bioavailability studies in support of Pharmaceutical Applications.

The scope of this document is limited to immediate-release and solid oral pharmaceutical pharmaceutical products that are intended to deliver medication to the systemic circulation.

NDA has identified the Active Pharmaceutical Ingredients (APIs) that are eligible for a BCS- based biowaiver application. Therefore, in some cases it is not necessary to provide data to support the BCS classification of the respective API(s) in the application i.e. data supporting the Pharmaceutical Product solubility or permeability class.

2.1 BCS Classification and Eligibility of a Pharmaceutical Product

A biowaiver based on the BCS considers:

a) the solubility and permeability of the API;

b) the similarity of the dissolution profiles of the multisource and comparator products in pH 1.2, 4.5 and 6.8 media (see below);

c) the excipients used in the formulation (see below); and

d) the risks of an incorrect biowaiver decision in terms of the therapeutic index of, and clinical indications for, the API (for cases where an in vivo study would be required to demonstrate bioequivalence).

A pharmaceutical product is eligible for a BCS-based biowaiver providing:

a) The Pharmaceutical Product(s) satisfy the criteria outlined in these guidelines;

b) The pharmaceutical product is a conventional, immediate-release solid oral dosage form; and

c) The pharmaceutical product is the same dosage form as the comparator product (e.g., a tablet versus a tablet).

Biowaivers based on BCS can be granted under the following conditions:

a) Dosage forms containing APIs which are highly soluble, and highly permeable (i.e. BCS class I), and are rapidly dissolving are eligible for a biowaiver based on the BCS provided:

i. the dosage form is ***rapidly dissolving*** (as defined in the Dissolution Guideline, i.e. no less than 85 % of the labelled amount of the API dissolves in 30 minutes) and

ii. the dissolution profile of the multisource product is similar to that of the reference product at pH 1,2, pH 4,5 and pH 6,8 buffer using the paddle method at 75 rpm or the basket method at 100 rpm (as described in the Dissolution Guideline) and meets the criteria of dissolution profile similarity, f2 ≥ 50 (or equivalent statistical criterion). If both the comparator and the generic dosage forms are ***very rapidly dissolving***, i.e. 85 % or more dissolution at 15 minutes or less in all 3 media under the above test conditions, the two products are deemed equivalent and a profile comparison is not necessary.

b) The appropriateness of the biowaiver is addressed, i.e. confirmation with supporting references, that no characteristic which requires an ***in vivo*** bioequivalence study is applicable. In addressing the appropriateness of the BCS biowaiver the benefit-risk balance / ratio, clinical indications, food effect and any other relevant aspect should be included. ***Reference 12, WHO Technical Report Series 937 Annex 7 Section 9.2 and Annex 8 or the latest revision.***

Omission of BE studies must be justified. Generally, BE studies are not necessary if a product fulfils one or more of the following conditions:

a) Solutions, complex or simple, which do not contain any ingredient which can be regarded as a pharmacologically active substance;

b) Haemodialysis solutions and peritoneal dialysis solutions;

c) 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;

d) 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);

e) Products that are powder for reconstitution as a solution and the solution meets either criterion (c) or (d) above;

f) Oral immediate release tablets, capsules and suspensions containing drug substances with high solubility and high permeability and where the pharmaceutical product has a high dissolution rate, provided the applicant submits an acceptable justification for not providing bioequivalence data;

g) Oral solutions containing the same active ingredient(s) in the same concentration as a currently registered oral solution and not containing excipients that may significantly affect gastric passage or absorption of the active ingredient(s);

h) Products for topical use provided the product is intended to act without systemic absorption when applied locally;

i) 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;

j) Otic or ophthalmic products prepared as aqueous solutions and containing the same drug substance(s) in the same concentration.

k) The product is a solution intended solely for intravenous administration.

l) The product is to be parenterally or orally administered as a solution.

m) The product is an oral solution, syrup, or other similarly solubilised form;

n) 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.

o) The product is a solution intended for ophthalmic or otic administration.

p) The product is an inhalant volatile anesthetic solution, Inhalation and nasal preparations.

q) The product is a reformulated product by the original manufacturer that is identical to the original product except for coloring agents, flavoring agents or preservatives, which are recognized as having no influence upon bioavailability.

r) Gases.

s) Solutions for oral use which contain the active substance(s) in the same concentration as the innovator product and do not contain an excipient that affects gastro-intestinal transit or absorption of the active substance.

t) Powders for reconstitution as a solution and the solution meets the criteria indicated in (k) above.

Additional information on several dosage forms

Solutions: Pharmaceutically equivalent solutions for oral use (including syrups, elixirs, tinctures or other soluble forms but not suspensions), containing the active pharmaceutical ingredient in the same molar concentration as the comparator product, and containing only excipient(s) known to have no effect on gastrointestinal (GI) transit, GI permeability and hence absorption or stability of the active pharmaceutical ingredient in the GI tract are considered to be equivalent without the need for further documentation.

Pharmaceutically equivalent powders for reconstitution as solution, meeting the solution criteria above, are considered to be equivalent without the need for further documentation.

Suspensions: Bioequivalence for a suspension should be treated in the same way as for immediate release solid oral dosage forms.

Fixed-dose combination products (including co-packaged products): Combination products should in general be assessed with respect to bioavailability and bioequivalence of APIs either separately (in the case of a new combination) or as an existing combination. The study in case of a new combination should be designed in such a way that the possibility of a pharmacokinetic and / or pharmacodynamic active-active interaction could be detected.

In general approval of FDC will be considered in accordance with the WHO Technical report series 929 “Guidelines for registration of fixed-dose combination pharmaceutical products 2005” or the latest revision and FDA “Guidance for Industry: Fixed Dose Combinations, Co- Packaged Drug Products, and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment of HIV” October 2006 or the latest revision.

Medicines Intended for Local Action: Non-solution pharmaceutical products, which are for non-systemic use (oral, nasal, ocular, dermal, rectal, vaginal, etc., application) and are intended to act without systemic absorption. In these cases, the bioequivalence is established through comparative clinical or

pharmacodynamic, dermatopharmacokinetic studies and/or ***in vitro*** studies. In certain cases, active concentration measurement may still be required for safety reasons in order to assess unintended systemic absorption.

Parenteral Solutions: It is incumbent upon the applicant to demonstrate in the dossier (not in the BE report) that the excipients in the pharmaceutically equivalent product are essentially the same and in comparable concentrations as those in the reference product. In the event that this information about the reference product cannot be provided by the applicant, it is incumbent upon the applicant to perform ***in vivo*** or ***in vitro*** studies to demonstrate that the differences in excipients do not affect product performance.

The influence of pH on precipitation should be clearly addressed and the absence of formation of sub-visible particulate matter over the physiological pH range be demonstrated.

Parenteral Aqueous solutions and Powders for reconstitution to be administered by parenteral routes (intravenous, intramuscular, subcutaneous) containing the same active pharmaceutical ingredient(s) in the same molar concentration and the same or similar excipients in comparable concentrations as the comparator product are considered to be equivalent without the need for further documentation.

Certain excipients (e.g. buffer, preservative, antioxidant) may be different provided the change in these excipients is not expected to affect the safety and/or efficacy of the medicine product.

Other parenterals bioequivalence studies are required. For intramuscular dosage forms, monitoring is required until at least 80 % of the AUC~ has been covered.

Topical Products: Pharmaceutically equivalent topical products prepared as aqueous solutions containing the same active pharmaceutical ingredient(s) in the same molar concentration and essentially the same excipients in comparable concentrations are considered to be equivalent without the need for further documentation.

It is incumbent upon the applicant to demonstrate in the dossier (not in the BE report) that the excipients in the pharmaceutically equivalent product are essentially the same and in comparable concentrations as those in the reference product. In the event that this information about the reference product cannot be provided by the applicant, it is incumbent upon the applicant to perform ***in vivo*** or ***in vitro*** studies to demonstrate that the differences in excipients do not affect product performance.

Topical Products for Local Action: The human vasoconstrictor test (blanching test) is recommended to prove bioequivalence of other topical preparations containing corticosteroids intended for application to the skin and scalp. Validated visual and/or chromometer data will be necessary.

Simple topical solutions with bacteriostatic, bactericidal, antiseptic and/or antifungal claims may qualify for a waiver based on appropriate validated ***in vitro*** test methods, e.g. microbial growth inhibition zones.

For other topical formulations clinical data (comparative clinical efficacy) will be required.

Proof of release by membrane diffusion will not be accepted as proof of efficacy, unless data are presented that show a correlation between release through a membrane and clinical efficacy.

Whenever systemic exposure resulting from locally applied/locally acting pharmaceutical products entails a risk of systemic adverse reactions, systemic exposure should be measured.

Topical Products for Systemic Action: For other locally applied products with systemic action, e.g. transdermal products, a bioequivalence study is always required.

Otic and ophthalmic products: Pharmaceutically equivalent otic or ophthalmic products prepared as aqueous solutions and containing the same active pharmaceutical ingredient(s) in the same molar concentration and essentially the same excipients in comparable concentrations are considered to be equivalent without the need for further documentation.

Certain excipients (e.g. preservative, buffer, substance to adjust tonicity or thickening agent) may be different provided use of these excipients is not expected to affect safety and/or efficacy of the product.

Aerosols, nebulisers, nasal sprays: Pharmaceutically equivalent solutions for aerosol or nebuliser inhalation or nasal sprays, tested to be administered with or without essentially the same device, prepared as aqueous solutions, containing the same active pharmaceutical ingredient(s) in the same concentration and essentially the same excipients in comparable concentrations are considered to be equivalent without the need for further documentation.

The pharmaceutical product may include different excipients provided their use is not expected to affect safety and/or efficacy of the product.

Particle size distribution may be used in support of proof of efficacy for inhalations. The Anderson sampler or equivalent apparatus should be used. In addition, appropriate information should be submitted to provide evidence of clinical safety and efficacy.

Gases: Pharmaceutically equivalent gases are considered to be equivalent without the need for further documentation.

Miscellaneous Oral Dosage Forms

Pharmaceutical products subject to buccal or sublingual absorption are not eligible for a biowaiver application. Rapidly dissolving pharmaceutical products, such as

buccal and sublingual dosage forms, should be tested for ***in vitro*** dissolution and ***in vivo*** BA and/ or BE. Chewable tablets should also be evaluated for in vivo BA and/or BE. Chewable tablets (as a whole) should be subject to ***in vitro*** dissolution because a patient, without proper chewing, might swallow them. In general, ***in vitro*** dissolution test conditions for chewable tablets should be the same as for non-chewable tablets of the same API/moiety.

Modified Release Products

Modified Release Products include delayed release products and extended (controlled) release products (as defined in the P&A guideline). In general, bioequivalence studies are required.

a) Beaded Capsules - Lower Strength: For extended release beaded capsules where the strength differs only in the number of beads containing the API, a singledose, fasting BE study should be carried out on the highest strength. A biowaiver for the lower strength based on dissolution studies can be requested. Dissolution profiles in support of a biowaiver should be generated for each strength using the recommended dissolution test methods and media described in the Dissolution guideline.

b) Extended release tablets - Lower strength: For extended release tablets when the pharmaceutical product is:

   i. in the same dosage form but in a different strength, and

   ii. is proportionally similar in its APIs and IPIs, and

   iii. has the same drug/API release mechanism,

   an ***in vivo*** BE determination of one or more lower strengths may be waived based on dissolution testing as previously described. Dissolution profiles should be generated on all the strengths of the test and the reference products.

When the highest strength (generally, as usually the highest strength is used unless a lower strength is chosen for reasons of safety) of the multisource product is bioequivalent to the highest strength or dose[7] of the reference product, and other strengths are proportionally similar in formulations and the dissolution profiles are similar between the dosage strengths, biowaiver can be considered to lower / other strengths.

Products Intended for Other Routes of Administration

It is incumbent upon the applicant to demonstrate in the dossier (not in the BE report) that the excipients in the pharmaceutically equivalent product are

[7] Dose included in the dosage range of the NDA approved package insert of the innovator product registered in Uganda.

essentially the same and in comparable concentrations as those in the reference product. In the event that this information about the comparator product cannot be provided by the applicant, it is incumbent upon the applicant to perform in vivo or in vitro studies to demonstrate that the differences in excipients do not affect product performance.

BIOWAIVER REQUIREMENTS

In order for a pharmaceutical product to qualify for a biowaiver, criteria with respect to the composition and ***in vitro*** dissolution performance of the pharmaceutical product should be satisfied. The pharmaceutical product acceptance requirements are described below.

The pharmaceutical products are classified in BCS on the basis of following parameters:

a) Solubility

b) Permeability

c) Dissolution

Class Boundaries

a) A drug substance is considered HIGHLY SOLUBLE when the highest dose strength is soluble in < 250 ml water over a pH range of 1 to 7.5.

b) A drug substance is considered HIGHLY PERMEABLE when the extent of absorption in humans is determined to be > 90% of an administered dose, based on mass- balance or in comparison to an intravenous reference dose.

c) A drug product is considered to be RAPIDLY DISSOLVING when > 85% of the labeled amount of drug substance dissolves within 30 minutes using USP apparatus I or II in a volume of < 900 ml buffer solutions.

Solubility Determination

pH-solubility profile of test drug in aqueous media with a pH range of 1 to 7.5. Shake-flask or titration method.

Analysis by a validated stability-indicating assay.

Permeability Determination

a) Extent of absorption in humans:

   i. Mass-balance pharmacokinetic studies.

   ii. Absolute bioavailability studies.

   iii. Intestinal permeability methods:

b) In vivo intestinal perfusions studies in humans.

i. In vivo or in situ intestinal perfusion studies in animals.

ii. In vitro permeation experiments with excised human or animal intestinal tissue.

iii. In vitro permeation experiments across epithelial cell monolayers.

The BCS categorizes Pharmaceutical Products into one of four BCS classes based on these characteristics. For the purposes of these guidelines, Pharmaceutical Products are classified as follows:

Class I: high solubility, high absorption

Class II: low solubility, high absorption

Class III: high solubility, low absorption

Class IV: low solubility, low absorption

BCS-based biowaiver applications will only be considered for immediate-release solid oral dosage forms containing eligible Pharmaceutical Products if the required data, as described in these guidelines, ensures the similarity between the proposed pharmaceutical product and the appropriate comparator product.

If a BCS-based biowaiver is granted and the product subsequently fails a bioequivalence test, this must be reported immediately with an assessment of the failure.

BCS Class 1 Pharmaceutical Products

Although the assessment of the potential impact of excipients on absorption would be simplified if the excipients employed in the proposed product are qualitatively the same and quantitatively similar to those in the comparator product, some differences in formulation are permitted except in excipients affecting bioavailability as discussed above. When there are differences in excipients between the test and comparator product, a justification should provide information on attempts and challenges encountered with the use of qualitatively and quantitatively similar excipients.

BCS Class III Pharmaceutical Products

Excipients in the proposed product formulation should be qualitatively the same and quantitatively very similar to that of the comparator product as per the proportionality policy.

Batch requirements

The batches of pharmaceutical product used for all biowaiver testing should, at a minimum, conform to the requirements for the 'biobatch' employed in ***in vivo*** comparative bioavailability trials designed to demonstrate the bioequivalence of a pharmaceutical product to a comparator product. Pilot scale batches must be at least 100,000 units or 1/10 the size of commercial scale, whichever is greater.

The measured Pharmaceutical Product content of the batches employed must meet requirements with respect to label claim, and the content should be within 5% of the measured content of the comparator product batch(es) used in comparative testing.

For higher risk pharmaceutical products meeting either of the following conditions, biowaiver testing should be conducted with at least one batch of production (commercial) scale:

a) The product is a low dose form, when the tablet/capsule strength is 5 mg or lower and/ or the Pharmaceutical Product forms 2% weight per weight (w/w) or less of the total mass of the tablet/capsule content; or

b) When the chosen manufacturing process is prone to variability and/or scale-up difficulties (e.g., direct compression process for manufacturing a low dose product); complex (e.g., use of coating technology to add the Pharmaceutical Product to inert granules, lyophilisation, microencapsulation); and/or uses new technologies (e.g., nanotechnology).

3.0 ADMINISTRATIVE BIOWAIVER REQUIREMENTS

3.1 Trade name of the test product:

Trade/Proprietary name means the (trade or brand) name which is unique to a particular pharmaceutical product and by which it is generally identified (and by which it is registered in the country of manufacture).

3.2 INN of active ingredient(s):

Approved / INN / generic name in relation to a pharmaceutical product means the internationally recognised non-proprietary name of such a drug or such other name as the PPB may determine.

3.3 Dosage form and strength

Dosage form of the product shall mean the form in which the pharmaceutical product is presented, e.g. solution, suspension, eye drops, emulsion, ointment, suppository, tablet, capsule, etc. For injections, the type of presentation (e.g. vial, ampoule, dental cartridge, etc), and the type of content (eg. powder for reconstitution, solution, suspension, oily solution, etc.) shall also be stated.

Strength of a pharmaceutical product shall be given per unit dosage form or per specified quantity: e.g. mg per tablet, mg per capsule, mg/mL, mg per 5mL spoonful, mg per G, etc.

3.4 Name of applicant and official address

The application for the registration of a drug shall be made only by:

a) the License/patent holder

b) the manufacturer

c) an authorised Local Technical Representative (LTR) of the manufacturer or License/ patent holder

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

3.5 Name of manufacturer of finished product

Provide the name of manufacturer of finished product and full physical address of the manufacturing site. The name, physical address, telephone number, fax number, and e-mail address of the manufacturer shall be provided. Where different activities of manufacture of a given product are carried out at different manufacturing sites, the above particulars shall be provided for each site and the activity carried out at the particular site shall be stated as shown in the table below.

Name of the Manufacturer	Full Physical address of the Manufacturing Site	Activity at the site

A copy of a valid manufacturing License shall be provided for each site. Only products entirely manufactured at sites that meet PPB's requirements for current Good Manufacturing Practice shall be eligible for registration.

3.6 Name of the Laboratory or Contract Research Organisation(s)

Name and address of the laboratory or Contract Research Organisation(s) where the BCS- based biowaiver dissolution studies were conducted.

4.1 TEST PRODUCT

There should be a tabulation of the composition of the formulation(s) proposed for marketing and those used for comparative dissolution studies

a) Please state the location of the master formulae in the specific part of the dossier) of the submission.

b) Tabulate the composition of each product strength using the table 2.1.1

c) 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/ hard gelatine capsule, if any.

d) Biowaiver batches should be at least of pilot scale (10% of production scale or capsules or tablets whichever is greater) and manufacturing method should be the same as for production scale.

If the formulation proposed for marketing and those used for comparative dissolution studies are not identical, copies of this table should be filled in for each formulation with clear identification in which study the respective formulation was used. Provide a comparison of unit dose compositions (if compositions are different) equivalence of the compositions or justified differences

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.

Well-established excipients in usual amounts should be employed in the proposed pharmaceutical product. A description of the function and a justification for the relative amount of each excipient is required. Excipients that might affect the bioavailability of the Pharmaceutical Product e.g., mannitol, sorbitol, or surfactants, should be identified and their impact discussed. These critical excipients should not differ qualitatively or quantitatively between the test product and comparator product.

5.0 COMPARATOR PRODUCT

Comparator product: Enclose a copy of product labelling (summary of product characteristics), as authorized in country of purchase, and translation into English, if appropriate.

Provide the name and manufacturer of the comparator product including full physical address of the manufacturing site)

Provide the qualitative (and quantitative, if available) information on the composition of the comparator product

Tabulate the composition of the comparator product based on available information and state the source of this information.

Provide relevant copies of documents (e.g. receipts) proving the purchase, shipment and storage of the comparator product

Provide the 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.

6.0 COMPARISON OF TEST AND COMPARATOR PRODUCTS

6.1 Formulation

6.1.1 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.

6.1.2 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.

6.1.3 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

7.0 IN VITRO DISSOLUTION

The applicant shall provide complete information on the critical quality attributes of the Pharmaceutical Product and finished product for both the test and comparator product including, but not limited to: polymorphic form; enantiomeric purity; partition coefficient; acid, base, amphoteric or neutral nature; dissociation constant (pKa); and any information on bioavailability or bioequivalence problems with the substance or pharmaceutical product, including literature surveys and applicant derived studies. All study protocols including standards, quality assurance and testing methods must be appropriately detailed and validated according to current regulatory guidelines's and policies.

Information regarding the comparative dissolution studies should be included to provide adequate evidence supporting the biowaiver request. State the location of:

a) the dissolution study protocol(s) in this biowaiver application

b) the dissolution study report(s) in this biowaiver application

c) the analytical method validation report in this biowaiver application

7.1 Test Conditions

The following conditions should be employed in the comparative dissolution studies to characterise the dissolution profile of the product. A profile of the solubility of the Pharmaceutical Product should be developed for the physiological pH range of 1.2 - 6.8 employing the following conditions:

a) Amount: One unit of the strength for which a biowaiver is requested with the highest dose of the Pharmaceutical Product being used.

b) Methodology: Basket apparatus (USP I), paddle apparatus (USP II) or similar method with justification

c) Agitation: Paddle apparatus at 50 revolutions per minute (rpm) or basket apparatus at 100 rpm

d) Dissolution media: Provide the composition, temperature, volume, and method of de-aeration. At a minimum, Aqueous buffers solutions of pH 1.0 - 1.2, 4.5, 6.8, and at the pKa of the Pharmaceutical Product (if within pH range of 1.2-6.8). The pH for each test solution should be confirmed before

and after the addition of the Pharmaceutical Product in order to ensure pH stability of the buffered medium.

e) Volume of media: ≤ 900 mL

f) Sample collection system: Provide Sample collection system: method of collection, sampling times, sample handling and storage. At a minimum the following sampling times points 10, 15, 20 and 30 minutes.

g) Temperature of media: 37 ± 1°C

h) Replicates: Not less than 12 units per batch at each pH medium tested

7.1.1 Additional information

Dissolution tests should be conducted using fully validated dissolution methods and analytical techniques. Care should be taken to ensure the pH of the medium is maintained throughout each trial. To prevent continued dissolution, collected samples should be filtered immediately. Additional testing may be required under the pH conditions within the range of 1.0 - 6.8 at which the Pharmaceutical Product displays minimum solubility.

Simulated gastric fluid without enzymes may be employed in lieu of the pH 1.2 buffer [or 0.1 N hydrochloride (HCl)] medium, and in the same fashion, simulated intestinal fluid without enzymes may be employed in lieu of the pH 6.8 buffer medium. Surfactants should not be employed in dissolution testing for a BCS-based biowaiver. The use of enzymes may be justified when gelatin capsules or tablets with a gelatin coating are being compared.

At least 12 units should be used for each profile determination. Mean dissolution values can be used to estimate the similarity factor, f2. To use mean data, the percent coefficient of variation at the earlier point should be not more than 20% and at other time points should be not more than 10%. Because f2 values are sensitive to the number of dissolution time points, only one measurement should be included after 85% dissolution of the product. Compilation of historical data is not acceptable.

7.1.2 Proportionally similar formulations

A prerequisite for qualification for a biowaiver based on dose-proportionality of formulations is that the generic product at one strength has been shown to be bioequivalent to the corresponding strength of the reference product.

a) the further strengths of the generic product are proportionally similar in formulation to that of the studied strength.

b) When both of these criteria are met and the dissolution profiles of the further dosage strengths are shown to be similar to the one of the studied strength on a percentage released vs. time basis, the biowaiver procedure can be considered for the further strengths.

When the pharmaceutical product is the same dosage form but of a different strength and is proportionally similar in its API, a biowaiver may be acceptable.

7.2 Summary of the results

Provide a summary of the dissolution conditions and method described in the study report(s). The summary provided 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.

Comparative ***in vitro*** dissolution tests should be conducted using a minimum of two batches of each of the proposed product and comparator product. For biowaiver purposes the dissolution profiles, in three media of the test and the comparator product should be tested for similarity.

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.

7.3 Discussions and conclusions

Provide discussions and conclusions taken from dissolution study(s) in form of a summary statement of the studies performed.

The reporting format should include tabular and graphical presentations showing individual and mean results and summary statistics. The tabular presentation should include standard deviation (SD) and coefficient of variation.

The report should include an identification of all excipients, and qualitative and quantitative differences between the test and comparator products with comments on how these excipients or differences may impact dissolution and ***in vivo*** absorption.

A full description of the analytical methods employed, including validation, should be provided.

A detailed description of all test methods and solutions, including test and reference batch information [unit dose (mg and %), batch number, manufacturing date and batch size where known, expiry date, and any comments] examined is required. The dissolution report should also include information on the dissolution conditions such as apparatus, de-aeration, filtration process during sampling, volume, etc.

The f_2 similarity factor should be used to compare dissolution profiles from different products and/or strengths of a product. An f_2 value >50 indicates a sufficiently similar dissolution profile such that further ***in vivo*** studies are not necessary. For an f_2 value < 50, it may be necessary to conduct an ***in vivo*** study. However, when both test and reference products dissolve 85% or more of the label amount of the API in 5 minutes, similarity is accepted without the need to calculate f_2 values.

If an application is submitted to NDA subsequent to that of either the European Medical Association (EMA) or United States FDA, the reporting format can be identical to that of those agencies; however, the information provided must be consistent with the requirements of these guidelines.

7.3.1 Acceptance criteria

BCS Class I Pharmaceutical Products: The test product and comparator product should display either very rapid or similarly rapid ***in vitro*** dissolution characteristics (> 85% dissolved in ≤ 30 minutes) under the defined conditions in order to be eligible for a biowaiver. The similarity of dissolution profiles are demonstrated when the f2 value is ≥ 50. Profile comparison (f2 testing) is not necessary for very rapidly dissolving products (> 85% dissolved in ≤ 15 minutes). BCS Class III Pharmaceutical Products: The test product and comparator product should display very rapid ***in vitro*** dissolution (> 85% dissolved in ≤ 15 minutes) characteristics under the defined conditions in order to be eligible for a biowaiver.

7.3.2 Additional Strengths of a Pharmaceutical Product

When equivalence to a comparator product for one strength in a series of strengths is established on the basis of a BCS-based biowaiver, a waiver from the requirement for conducting studies with other strengths cannot then be granted based on the proportionality principles as described in NDA's requirements on Bioequivalence. Other strengths in the product line must conform to the requirements for a BCS-based biowaiver in comparison to the pharmaceutically equivalent comparator product of the same strength.

8.0 QUALITY ASSURANCE

Provide the internal quality assurance methods stating the location in the biowaiver application where internal quality assurance methods and results are described for each of the study sites.

8.1 Internal quality assurance methods

Provide the internal quality assurance methods and results are described for each of the study sites.

8.2 Monitoring, Auditing and Inspections

Provide a list of all auditing reports of the study, and of recent inspections of study sites by regulatory agencies. Provide the respective reports for each of the study sites e.g., analytical laboratory, laboratory where dissolution studies were performed.

9.0 DECLARATION

The declaration must be signed, dated and authenticated by an Official stamp. No Applications will be evaluated without authenticated declaration.

APPENDIX 14: BCS BIOWAIVER APPLICATION FORM

Biopharmaceutics Classification System (BCS)

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

NDA has identified the Active Pharmaceutical Ingredients (APIs) that are eligible for a BCS- based biowaiver application. Therefore, in some cases it is not necessary to provide data to support the BCS classification of the respective API(s) in the application i.e. data supporting the drug substance solubility or permeability class.

General Instructions:

a) Please review all the instructions thoroughly and carefully prior to completing the current Application Form.

b) Provide as much detailed, accurate and final information as possible.

c) Please enter the data and information directly following the greyed areas.

d) 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.

e) Please provide the document as an MS Word file.

f) Do not paste snap-shots into the document.

g) The appended electronic documents should be clearly identified in their file names, which should include the product name and Annex number.

h) Before submitting the completed Application Form, kindly check that you have provided all requested information and enclosed all requested documents.

i) Should you have any questions regarding this procedure, please contact the NDA Secretariat.

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 NDA.

1.0 Administrative data

1.1	**Trade name of the test product**
1.2	**INN of active ingredient(s)**
< Please enter information here >	
1.3	**Dosage form and strength**
< Please enter information here >	
1.4	**Product Reference number**
< Please enter information here >	
1.5	**Name of applicant and official address**
< Please enter information here >	
1.6	**Name of manufacturer of finished product and full physical address of the manufacturing site**
< Please enter information here >	
1.7	**Name and address of the laboratory or Contract Research Organisation(s) where the BCS-based biowaiver dissolution studies were conducted.**
< Please enter information here >	

2.0 Test product

2.1 Tabulation of the composition of the formulation(s) proposed for marketing and those used for comparative dissolution studies

a) Please state the location of the master formulae in the specific part of the dossier) of the submission.

b) Tabulate the composition of each product strength using the table 2.1.1

c) For solid oral dosage forms the table should contain only the ingredients in tablet

d) core or contents of a capsule. A copy of the table should be filled in for the film coating/hard gelatine capsule, if any.

e) Biowaiver batches should be at least of pilot scale (10% of production scale or

f) 100,000 capsules or tablets whichever is greater) and manufacturing method should be the same as for production scale.

Please note: If the formulation proposed for marketing and those used for comparative dissolution studies are not identical, copies of this table should be filled in for each formulation with clear identification in which study the respective formulation was used

2.1.1 ***Composition of the batches used for comparative dissolution studies***				
Batch number				
Batch size (number of unit doses)				
Date of manufacture				
Comments, if any				
Comparison of unit dose compositions (duplicate this table for each strength, if compositions are different)				
Ingredients (Quality standard)	Unit dose	Unit dose (%)		
Equivalence of the compositions or justified differences				

2.2 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 >

COMMENTS FROM REVIEW OF SECTION 2.0 - NDA USE ONLY

3.0 Comparator product

3.1 Comparator product

Please enclose a copy of product labelling (summary of product characteristics), as authorized in country of purchase, and translation into English, if appropriate.

3.2 Name and manufacturer of the comparator product (Include full physical address of the manufacturing site)

< Please enter information here >

3.3 Qualitative (and quantitative, if available) information on the composition of the comparator product

Please tabulate the composition of the comparator product based on available information and state the source of this information.

3.3.1 Composition of the comparator product used in dissolution studies		
Batch number		
Expiry date		
Comments, if any		
Ingredients and reference standards used	Unit dose (mg)	Unit dose (%)

3.4 Purchase, shipment and storage of the comparator product

Please attach relevant copies of documents (e.g. receipts) proving the stated conditions.

< Please enter information here >

3.5 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 >

COMMENTS FROM REVIEW OF SECTION 3.0 - NDA USE ONLY

4.0 Comparison of test and comparator products

4.1 Formulation

4.1.1 Identify any excipients present in either product that are known to impact on in vivo absorption processes 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.
< Please enter information here >

4.2 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.
< Please enter information here >

4.3 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

< Please enter information here >

COMMENTS FROM REVIEW OF SECTION 4.0 - NDA USE ONLY

5.0 Comparative in vitro dissolution Information regarding the comparative dissolution studies should be included below to provide adequate evidence supporting the biowaiver request. Comparative dissolution data will be reviewed during the assessment of the Quality part of the dossier. Please state the location of: a) the dissolution study protocol(s) in this biowaiver application b) the dissolution study report(s) in this biowaiver application c) the analytical method validation report in this biowaiver application
< Please enter information here >

5.1 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.

5.1.1 Dissolution media: Composition, temperature, volume, and method of de-aeration
< Please enter information here >

5.1.2 Type of apparatus and agitation speed(s) employed
< Please enter information here >

5.1.3 Number of units employed
< Please enter information here >

5.1.4 Sample collection: method of collection, sampling times, sample handling and storage
< Please enter information here >

5.1.5 Deviations from sampling protocol
< Please enter information here >

5.1.6 Dissolution media: Composition, temperature, volume, and method of de-aeration
< Please enter information here >

5.2 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 >

5.3 Provide discussions and conclusions taken from dissolution study(s) Please provide a summary statement of the studies performed.
< Please enter information here >

COMMENTS FROM REVIEW OF SECTION 5.0 - NDA USE ONLY

6.0 Quality assurance

6.1 Internal quality assurance methods Please state location in this biowaiver application where internal quality assurance methods and results are described for each of the study sites.
< Please enter information here >

6.2 Monitoring, Auditing, Inspections Provide a list of all auditing reports of the study, and of recent inspections of study sites by regulatory agencies. State locations in this biowaiver application of the respective reports for each of the study sites e.g., analytical laboratory, laboratory where dissolution studies were performed.
< Please enter information here >

COMMENTS FROM REVIEW OF SECTION 5.0 - NDA USE ONLY

Declaration

I, the undersigned, certify that the information provided in this application and the attached document is correct and true.

Signed on behalf of <company>

Date

Name and title

< Please enter information here >

CONCLUSIONS AND RECOMMENDATIONS – NDA USE ONLY

APPENDIX 15: BIOWAIVER APPLICATION FORM: ADDITIONAL STRENGTH

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

A request for a waiver from the requirement for conducting bioequivalence studies on additional strengths of the product submitted for assessment to the NDA can be made based on the proportionality of the formulations of the series of strengths. If additional strengths are proposed and a biowaiver for these strengths is sought, the following information should be provided.

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:

a) Please review all the instructions thoroughly and carefully prior to completing the current Application Form.

b) Provide as much detailed, accurate and final information as possible.

c) Please enter the data and information directly following the greyed areas.

d) 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.

e) The appended electronic documents should be clearly identified in their file names, which should include the product name and Annex number.

f) Please provide the application form as an MS Word file.

g) Before submitting the completed Application Form, kindly check that you have provided all requested information and enclosed all requested documents.

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.

Administrative data

1	**INN of active ingredient(s)**
< Please enter information here >	
2	**Dosage form and strength**
< Please enter information here >	
3	**Dosage form and strength** *(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

a) Please state the location of the master formulae in the quality part of the submission.

b) 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.

c) 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 a) State whether the drug displays linear or non-linear pharmacokinetics b) 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. c) 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 >

COMMENTS FROM REVIEW OF SECTION 1.1 – 1.3 – NDA 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 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:

a) Batch number of biobatch

b) Justification for use of a batch other than the biobatch

c) Comparative dissolution data for batch employed vs. (historical data for) biobatch

d) 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 >

COMMENTS FROM REVIEW OF SECTION 2.1 – 2.3 – NDA 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 >

COMMENTS FROM REVIEW OF SECTION 3.1 – 3.2 – NDA USE ONLY

4. Comparative in vitro dissolution: Studies comparing different strengths of the test product

a) Comparative dissolution data will be reviewed during the assessment of the Quality part of the dossier.

b) 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.

c) 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:

a) the dissolution study protocol(s) in the dossier

b) the dissolution study report(s) in the dossier

c) 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 >

COMMENTS FROM REVIEW OF SECTION 4.1 – 4.4 – NDA 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

a) 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 comparator product as identified on the should be employed.

b) Comparative dissolution data will be reviewed during the assessment of the Quality part of the dossier.

c) As per the registration guideline, 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.

d) 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:

a) the dissolution study protocol(s) in the dossier
b) the dissolution study report(s) in the dossier
c) 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 >

5.4.1 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 the results of the dissolution study(s) Please provide a summary statement of the studies performed.
< Please enter information here >

COMMENTS FROM REVIEW OF SECTION 5.1 – 5.6 – NDA USE ONLY

CONCLUSIONS AND RECOMMENDATIONS – NDA USE ONLY

DOCUMENT REVIEW HISTORY

Date of revision	Revision number	Document Number	Author(s)	Changes made and reasons for revision
July 2006	0	Not on record-	Not on record	First issue
24th/06/2013	1	DAR/GDL/004	Apollo Angole Gabriel Kaddu	Changed the entire registration guidelines into the new CTD format which is a harmonised electronic dossier submission that is acceptable
1st March 2018	2	DAR/GDL/004	Eunice Nakimuli Michael Mutyaba Juliet Okecho	1. Updated the mission and vision; location address and logo; 2. Aligned the guideline with the EAC MRH guideline for product registration by including small editorial changes; 3. Added section 1.12 and 1.13 on requirements for periodic safety update reports and risk management plans; 4. Added more information under “procedure for submission of an application in CTD format” on page xx. 5. Revised Appendix for presentation of bioequivalence trial information.

Date of revision	Revision number	Document Number	Author(s)	Changes made and reasons for revision
15 Feb 2023	3	PAR/GDL/004	Eunice Nakimuli Kemigisha Agnes Dr. Juliet Awori Okecho	i. Title revised from "Guidelines on Submission of Documentation for Marketing Authorisation of a Pharmaceutical Product for Human Use" to "Guidelines on Submission of Documentation for Registration of a Pharmaceutical Product for Human Use in Uganda" ii. Changed from Marketing Authorization to Registration; and marketing authorization holder to Holder of a Certificate of Registration wherever applicable iii. Added description for product and pharmaceutical product iv. Revised medicinal product to pharmaceutical product in compliance with the NDA&A Act and Regulations

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