REPUBLIC OF KENYA

REGISTRATION OF DRUGS

GUIDELINES TO SUBMISSION OF APPLICATIONS

PHARMACY AND POISONS BOARD

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PREFACE

OBJECTIVE OF THE GUIDELINE

This guideline presents a common format for the preparation of a well-structured application that will be submitted to Pharmacy and Poisons Board. This format for presentation of technical documentation will significantly reduce the time and resources needed to compile applications for registration of pharmaceuticals and will in future ease the preparation of electronic submissions. Evaluation of dossiers and communication with the applicants will be facilitated by a standard document of common elements.

This revised guideline has been improved by giving more details on requirements for active pharmaceutical ingredients (APIs) as well as finished pharmaceutical products (FPPs). In addition, requirements on bioequivalence and bio-waver(s) have been updated in line with the current state of knowledge.

The improvements in this guideline are based on the World Health Organization (WHO) Guidelines on Submission of Documentation for Prequalification of Multi-source Finished Pharmaceutical Products and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for human use.

SCOPE OF THE GUIDELINE

This guideline primarily addresses the organisation of the information to be presented in registration applications for new pharmaceuticals (including biotechnology-derived products).

This guideline is not intended to indicate what studies are required. It merely indicates an appropriate format for the data that have been acquired. Applicants should not modify the overall organisation of the document as outlined in the guideline. However, in the Nonclinical and Clinical Summaries, applicants can modify individual formats if needed to provide the best possible presentation of the technical information, in order to facilitate the understanding and evaluation of the results.

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LIST OF ABBREVIATIONS

API:	Active Pharmaceutical Ingredient
ATC:	Anatomic Therapeutic Chemical classification
AUC:	Area under the plasma concentration time curve
BAN:	British Approved Name
BIOTECH:	Biotechnological Products
BP:	British Pharmacopoeia
BSE:	Bovine Spongiform Encephalopathy
CAS:	Chemical Abstract Service
CE:	Chemical Entities
CEP:	European Certificate of Suitability
Cmax:	Maximum plasma concentration
CoA:	Certificate of Analysis
CPP:	Certificate of Pharmaceutical Product
DMF:	Drug Master File
EC:	European Commission
EU:	European Union
FDC:	Fixed Dose Combination
FPP:	Finished Pharmaceutical Product
GMP:	Good Manufacturing Practice
HIV:	Human Immune-deficiency Virus
ICH:	International Conference on Harmonization
INN:	International Non-proprietary Name
JAN:	Japanese Accepted Name
JP:	Japanese Pharmacopoeia
LOD:	Loss on Drying
MedDRA:	Medical Dictionary for Drug Regulatory Authorities
NCE:	New Chemical Entities
NMT:	Not More Than
PhEur:	European Pharmacopoeia
PhInt :	International Pharmacopoeia
PIL :	Patient Information Leaflet
PPB:	Pharmacy and Poisons Board
QA:	Quality Assurance
RH:	Relative Humidity
SMACS:	Starting Materials Certification Scheme
SMF:	Site Master File
SPC	Summary of Product Characteristics
TRS:	Technical Report Series
TSE:	Transmissible Spongiform Encephalopathy
USAN:	United States Approved Name
USP:	United States Pharmacopoeia
WHO:	World Health Organization

GENERAL INFORMATION

INTRODUCTION

This guideline applies only to pharmaceutical products. In the case of other medicinal products such as **herbal products, food supplements** and **medical devices**, separate guidelines are available and these can be obtained from PPB offices.

This guideline provides recommendations for applicants preparing application for a Registration of Pharmaceutical Product for submission to the Pharmacy and Poisons Board (PPB). The document describes how to organise applications based on the World Health Organization (WHO) Guidelines on Submission of Documentation for Prequalification of Multi-source Finished Pharmaceutical Products and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines on the CTD.

According to this new format, each application is a collection of documents, grouped five modules, together with the associated technical guidelines, provides detailed information about the contents of an application. Applicants should not modify the overall organisation of this format.

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

This guideline prescribes the minimum information required for submission of dossiers and the evaluation of products will be based on this guideline. The technical content of the documents in the parts is outside the scope of this guideline. This guideline does not indicate the data or studies required; they merely indicate an appropriate format and organisation for the data that have been acquired.

However, since science is ever changing, PPB in the interest of patient safety and well being will not accept outdated methods and techniques and will evaluate products based on the current state of scientific knowledge and standards. Applicants are therefore encouraged to keep abreast with scientific developments and use current scientific information to develop and test their products.

Applicants are requested to carefully read this guideline, fill in application form, prepare dossiers and submit one original hard-copy and one electronic copy (in a Portable Document Format, PDF, on a CD-Rom) and **should include MS-Word document for Modules 1 and 2**, cross-referenced to the dossier by clearly indicating the title and section number of all the supporting documents.

All areas are to be filled out by the applicant **EXCEPT** where indicated by **blue areas which are for PPB Official Use Only!**

The guideline is divided into SIX Parts:

- General Information
- Module 1: Administrative information
- Module 2: Chemical, Pharmaceutical, Non-Clinical and Clinical Overviews and Summaries
- Module 3: Chemical and Pharmaceutical Documentation
- Module 4: Non-Clinical Reports for New Chemical Entities Only
- Module 5: Clinical Study Reports

The annexes are:

- Annex I: Application for Registration of a Drug – (Form 1, revised 2010)
- Annex II: Model Stability Report for Active Pharmaceutical Ingredients (APIs)
- Annex III: Model Stability Report for Finished Pharmaceutical Products
- Annex IV: Summary Product Characteristics

Should you have any questions regarding this guideline, please contact the Pharmacy and Poisons Board (PPB), drug registration department.

LANGUAGE

All applications and supporting documents shall be in English and legible. Where material is not originally in English, a copy in the original language and a full translation should be submitted, the accuracy of the translation is the responsibility of the applicant. Authentication of the translation has to be done at the nearest Kenyan Embassy or by the national drug regulatory authority of the country from where the document originates.

Reports submitted only in a language other than English will not be accepted.

DATA PRESENTATION

All data shall be presented on A4 and 80g/m^2 paper with readily readable letters of at least 12 font sizes. Every page shall be numbered sequentially and state the exact location (Annex number) of any appended documents in the relevant sections of the form. Before submitting the completed form, check that you have provided all requested information.
Extension sheets, tables, diagrams and other supporting documents shall as far as possible be of the same size, well annotated, numbered and appropriately cross-referenced. Acronyms and abbreviations should be defined the first time they are used in each part.
Every page should be numbered. Different sections of the dossier shall be distinctly marked and page numbered in the style: ***page x of y*** and have a table of contents indicating the sections and page numbers.
All parts must be **bound** and **arranged** sequentially**.** The left-hand margin should be sufficiently large that information is not obscured by the method of binding. The dossier covers shall be made of a material which is thick and hard enough not to collapse in standing position.
One or more dossier file may be used depending on the number of pages contained in each part and in this case the files shall be serially numbered in the format i.e. **FILE NO. X of Y.**

OFFICIAL REFERENCES AND TEXTS

References should be cited in accordance with the current edition of the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*, International Committee of Medical Journal Editors (ICMJE).

When direct reference is made to specifications, quality control procedures and test methods in official compendia, text books or standard publications, reprints or authenticated copies of relevant pages shall be enclosed. References to pharmacopoeias should specify the year of issue. References should be provided for all in-house processes.

There shall be no cross reference of particulars or documentation between one product and another.

SUBMISSION OF APPLICATION

The application should be submitted to the following address:

The Registrar,
Pharmacy and Poisons Board
Lenana Road,
P. O. Box 27663-00506,
NAIROBI.

For purposes of submission to PPB, applications are classified into three categories as follows:

New applications
This is an application for registration of a medicinal product that is intended to be placed on the Kenyan market for the first time.

A new application may only be made by the applicant and he/she shall be the person who signs the application form.

A separate application is required for each product. Products that differ in active ingredient(s), strength, dosage forms, proprietary names though containing the same ingredients, are considered to be different products and hence require separate applications.

However, products containing the same active ingredients and the same strength made by the same manufacturer at the same manufacturing site, to the same specifications and dosage form, but differing only in packing or pack sizes require only one application.

A new application for registration shall include submission of:

i. Two dully filled application forms (Original and Duplicate) and an electronic copy (a summary of the dossier contents) in MS Word on a CD-ROM of modules 1 and 2 only including their supporting documents - see Annex I

ii. Three (3) samples of the smallest commercial pack(s) from one batch with batch certificates of analysis.

iii. An original Certificate of Pharmaceutical Product (WHO Format) on official papers of the issuing competent drug regulatory authority.

iv. A site master file in case the product is manufactured at a plant(s) not inspected and approved by PPB.

v. Non refundable application fee for registration of medicines in Kenya and GMP inspection fees for facilities not yet inspected by PPB.

Applications for Renewal of Registration

Applications for renewal of registration shall be made at least 3 months before the expiry of existing registration by submitting the following:

i. Dully filled in application form for renewal of registration.
ii. Batch Manufacturing Record (BMR) of a real batch manufactured within at most six months before the submission of the application.
iii. Submit Periodic Safety Update Reports (PSUR)
iv. Proof of interchangeability for generics as explained in Module 5.
v. Any other requirements that the Board may determine.
vi. Three (3) samples of the smallest commercial pack(s) from the same batch along with batch certificates of analysis.
vii. A site master file in case the product is manufactured at a plant(s) not inspected and approved by PPB.
viii. Non refundable application fee for registration of medicines in Kenya and GMP inspection fees for facilities not inspected and approved by PPB, GMP department.

Application for Variation of a registered medicinal product

All applications for variation to a registered product shall be made according to requirements stipulated in the PPB Application Guideline for Variation of Registered Medicinal Products also available the PPB offices.

PAYMENT OF FEES

Every application shall be accompanied by appropriate fees at the time of application. Any application that will not be accompanied by appropriate fees will not be accepted.

Mode of Payment: Payments by crossed or bankers cheque shall be made payable to **PHARMACY AND POISONS BOARD**.

Application for registration of a pharmaceutical product:	
Imported in to Kenya	US$ 1000
Fully manufactured in Kenya	US$ 500
Application for renewal of registration of a pharmaceutical product:	
Imported into Kenya	US$ 500
Fully manufactured in Kenya	US$ 300

If an application for renewal is made after the expiration of the period of validity of the certificate of registration the application shall be considered as a fresh application using form 1 (revised 2009).- **see annex I**

Variations: With respect to any variations to an original application, a fee of US$ 200 must be paid.

Replacement of a Certificate: A fee of US$ 100 shall be paid for a replacement copy of a Certificate of Registration for a pharmaceutical product, if the original is defaced, damaged or lost. The copy shall be stamped "duplicate copy".

Appeal fee: With respect to an appeal to an original application, a fee of US$ 300 must be paid at the time of appeal. Any appeal that will not be accompanied by appropriate fees will not be evaluated.

Other Charges: The Pharmacy and Poisons Board may, at its own discretion, charge an applicant such costs as it may incur for carrying out any laboratory investigations prior to the registration of a product.

AN OUTLINE OF THE EVALUATION PROCESS

Receiving of new applications

An application consists of documentation in hard copies and electronic copy (a summary of the dossier contents), samples and fees. The application may be delivered physically along Lenana Road, Nairobi, Kenya. An application may only be received by PPB upon payment of the application fees.

Evaluation process

The evaluation of applications is done on a first in first out (FIFO) basis unless the product meets the fast track criteria as set out in this guideline.

An application may be fast tracked if the product is

- Locally manufactured in Kenya. Note that contract manufacturing outside Kenya by a Kenyan company will not render the product to be locally manufactured.
- A **Priority Medicine** i.e. the product is indicated for diseases which at the time of application have no registered alternative medicine or evidence has been submitted to show that the product has significant advantages in terms of safety and efficacy over existing products indicated for treatment or prevention of life threatening diseases.

Assessment of product dossiers involves evaluators from within or outside PPB. The evaluation report produced by the evaluator is reviewed by a second evaluator who does the quality assurance of the evaluation report and where necessary adds comments and finalizes the report and recommendations. Evaluation is done against the requirements of this guideline in accordance with the Standard Operating Procedures for Evaluation. However, the Board reserves the right to request any additional information to establish the quality, safety and efficacy of a medicine in keeping with the level of knowledge current at the time of evaluation.

During evaluation, additional data and/or samples may be requested through a query letter. Once a query has been raised and issued to the applicant, the process stops until when PPB receives a written response to the query. Conclusion of the application may only be made if responses to queries issued in the same letter are submitted in one transaction for consideration. Failure to comply with this condition or if the queries have been reissued for a second time and the applicant provides unsatisfactory responses, the product will be disqualified and the application will be rejected.

In the event the responses to the queries are not submitted within six months from the date they were issued, it will be deemed that the applicant has withdrawn the application. Thereafter, registration of the product may only be considered upon submission of a new application.

Pre-registration Laboratory analysis of the product sample

The samples will be analysed for all medicines and a certificate of analysis from a recognised Quality Control Laboratory in Kenya and within the region shall be submitted with the application (See section 1.13). Laboratory analysis of the samples will be done against the claimed in-house or pharmacopoeia specifications using the analytical method provided by the applicant.

The following Control Laboratories are recognised

- All WHO prequalified Laboratories in Kenya and within Eats African Community
- Drug Analysis Research Unit, DARU, of the School of Pharmacy, University of Nairobi

Please note that separate guideline for **post marketing surveillance** and **testing of every batch imported** into Kenya are available and can be obtained from PPB, pharmacovigilance department and NQCL offices.

Verification of compliance to current Good Manufacturing Practices (cGMP)

If the new application is from a new manufacturing site, PPB will conduct inspection of the site or use other means to verify whether the facility complies with current Good Manufacturing Practices Regulations and/or guideline before a product is registered. No product shall be registered unless the plant complies with cGMP.

After the inspection, the details of the observation made will be presented in a full report which will form part of the evaluation process.

When the facility is found not to comply with current GMP, the applicant will be required to rectify the observed deficiencies and submit a compliance report within a time frame agreed during the inspection. Based on the report, the Board may either approve the facility or conduct re-inspection.

If the applicant does not rectify and request for re-inspection within the 12 months or if after re-inspection the facility is found not to comply with cGMP, it will be deemed that the applicant has failed to rectify the deficiencies and has therefore withdrawn the respective application(s). The application will be rejected and thereafter registration of the product will only be considered upon submission of a new application.

Inspection of a facility for the purposes of considering applications for renewal of registration shall be done and if the facility is found not to comply with cGMP, registration of all products manufactured by the facility shall be withdrawn.

Consideration by Committee on Drug Registration
A summary of recommendations of evaluation, laboratory analysis and GMP status reports will be presented before the Committee on Drug Registration for consideration and making final recommendations for granting or rejecting registration of the product.

However, if there are unresolved safety, quality or efficacy issues the Committee may defer approval pending resolution of the issues. Should the applicant fail to provide the required data within six months, the product will be disqualified and the application will be rejected.

Registration will be granted by the board subject to the product complying with criteria prescribed under CAP 244, Pharmacy and Poisons Act. A certificate of marketing authorization together with applicable conditions shall be issued.

TIMELINES

The Board will implement the following timelines in processing applications for marketing authorization of pharmaceutical products.

Fast-tracked registration (Locally manufactured and Priority Medicines only), Post Approval Variation and Renewal of registration
Complete applications will be processed within 90 working days of receiving the application including evaluation of documentation and consideration by a committee on drug registration.

Evaluation of new applications
Complete new applications will be processed within 12 months of receipt of the application. The applicant will be required to provide any requested additional data within 6 months. In case additional time is required, a formal request must be submitted.

WITHDRAWAL OF OF AN APPLICATION

When the applicant fails to submit written responses to queries within 6 months from the date of their issuance, it will be deemed that the applicant has withdrawn the application or if the queries have been reissued for a second time and the applicant provides unsatisfactory responses, the product will be disqualified and the application will be rejected. The applicant will be required to apply afresh.

VALIDITY OF REGISTRATION

The registration of a pharmaceutical product shall be valid for five (5) years unless earlier suspended or revoked by PPB or withdrawn by applicant. The Board will give reasons in writing when it suspends or revokes, or amends conditions of registration. Likewise the applicant shall also give reasons for terminating registration of a product.

APPEALS

Any person aggrieved by a decision of PPB in relation to any application for marketing authorization of a pharmaceutical product may within two (2) months from the date of notice of the decision, make representations in writing to the Board and pay the requisite appeal fee and submitting additional data to support their representations.

MODULE 1: ADMINISTRATIVE INFORMATION

SECTION 1: ADMINISTRATIVE PARTICULARS OF THE PRODUCT

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

1.1 Applicant:
The application for the registration of a drug shall be made only by:

- the License/patent holder
- the manufacturer
- 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.

1.2 Trade/Proprietary name
Trade/Proprietary name means the (trade or brand) name which is unique to a particular drug and by which it is generally identified (and by which it is registered in the country of manufacture).The applicant should provide attached evidence from Kenya Industrial Property Institute, KIPI, in regard to the requirements for registration of Trademarks.

1.3 Approved / INN / generic name in relation to a drug
Approved / INN / generic name in relation to a drug means the internationally recognised non-proprietary name of such a drug or such other name as the PPB may determine.

1.4 Strength of the product
Strength of the 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.

1.5 Dosage form of the product
Dosage form of the product shall mean the form in which the drug is presented, eg. 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.

1.6 Packing/Pack size of the product
Packing/Pack size of the product shall mean the presentation of the product to be registered i.e. list all pack sizes intended for marketing. Pack size(s) for over the counter (OTC) product should be equivalent to a minimum full dose for the therapeutic indication.

1.7 Visual Description of the drug
Visual Description of the drug shall mean a full visual description of the drug including colour, size, shape and other relevant features, e.g. 'black and red gelatin capsule with marks "Amp -250", 'pink film-coated tablets with word "PAN" embossed on one side' etc.

1.8 Proposed Shelf life of the product
Proposed Shelf life of the product means the specified length of time prior to use for which pharmaceutical products are inherently subject to deterioration are deemed to remain fit for use under prescribed conditions

1.9 Pharmacotherapeutic group and ATC code
Specify clinical indication(s) which are supported by relevant information in Module 2 and 5 of the application dossier. The Anatomical Therapeutic Chemical (ATC) Classification System is used for the classification of drugs. The classification system divides drugs into different groups according to the organ or system on which they act and/or their therapeutic and chemical characteristics

Reference: *WHO Collaborating Centre for Drug Statistics Methodology: About the ATC/DDD system*

1.10 Legal Category

Indicate the proposed dispensing category/classification:

- Products subject to medical prescription or not subject to medical prescription
    - The product will be dispensed from Non-pharmacy outlets and pharmacies
    - The product will be dispensed from Pharmacies Only
- Products subject to medical prescription:
    - Controlled Drug Substance
    - Prescription Only Medicine, POM

1.11 Country of Origin

Country of Origin means the country of manufacture or production, of the medicine to be registered or country of product release.

1.12 Product Marketing Authorisation in the country of origin and other countries

The applicant shall provide the regulatory situation of the medicine to be registered in the country of origin and other countries. List the countries in which this product:

- Has been granted a marketing authorization. (Attach certificate of pharmaceutical product from the registering Authority)
- Has been withdrawn from any market;
- Where an application for marketing in any country has been rejected, suspended, deferred or withdrawn.

1.13 Pre-registration analysis of the product:

The Applicant must attach a certified copy of certificate from the National Quality Control Laboratory – Kenya or any other laboratory that the board may recommend. Proof of submission to National Quality Control Laboratory at the time of submission is allowed but the product will not be registered unless the certificate submitted. (See also the outline of the evaluation process described above)

1.14 Name and complete address(es)of the manufacturer(s) of the FPP

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.

1.15 GMP status of the Manufacturer and GCP/GLP status of the Clinical Research Organisation/ Laboratory

If the new application is from a new manufacturing site, PPB will conduct inspection of the site or use other means to verify whether the facility complies with current Good Manufacturing Practices (cGMP), Good Clinical Practices or Good Laboratory Practices, Regulations and/or guideline.

1.16 Local Technical Representative

Every applicant who is not resident in Kenya shall appoint ONE local technical representative who must be a company incorporated in Kenya and authorized by PPB to deal in medicinal products and must hold a wholesale dealers License. Evidence shall be made by submitting a power of attorney that complies with Kenyan laws.

The local technical representative shall be responsible for facilitating communication with the applicant and when the product is registered he shall assume all legal responsibilities regarding the product on the Kenyan market.

1.17 Summary Product Characteristics (SPC)

1.17.1 Product information for Health Professionals (For All Products subject to Medical Prescription)

Proposed Summary of product Characteristics (SPC – see Annex IV for structure) aimed at Medical practitioners and other health practitioners and approved by competent authority at the time of licensing. The SPC is an essentital part of registration and can only be changed with the consent of PPB
Reference: *"Guideline on summary of Product Characteristics – Notice to applicants", European commission, Enterprise Directorate – General, Pharmaceuticals and Cosmetics (Dec 1999)*

1.17.2 Patient information leaflet (For All Products not subject to Medical Prescription)

Provide copies of all package inserts and any information intended for distribution with the product to the patient. The patient information leaflet (PIL) should be in conformity with the SPC. It should be written in Kiswahili and/or English, should be legible, indelible and comprehensible.

Reference: http://pharmacos.eudra.org/F2/eudralex/vol-2/home.htm#2c

MODULE 2: CHEMICAL, PHARMACEUTICAL, NON-CLINICAL AND CLINICAL OVERVIEWS AND SUMMARIES

This section of the document (follows ICH: M4Q) and provides a harmonized structure and format for presenting CMC (Chemistry, Manufacturing and Controls) information in a registration dossier.

This section covers the chemical and pharmaceutical data including data for biological/ biotechnological products**.**

The table of contents includes sections on Drug Substance and Drug Product. A new section on Pharmaceutical Development has been included.

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

2.2 INTRODUCTION

The introduction should include proprietary name, non-proprietary name or common name of the drug substance, company name, dosage form(s), strength(s), route of administration, and proposed indication(s).

2.3 QUALITY OVERALL SUMMARY (QOS)

The Quality Overall Summary (QOS) is a summary that follows the scope and the outline of Module 3. The QOS should not include detailed information, data or justification that will be included in Module 3 or in other modules of the document.

The QOS should include sufficient information from each section to provide the Quality Evaluator with an overview of Module 3. The QOS should also emphasise critical key parameters of the product and provide, for instance, justification in cases where guideline 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, including cross-referencing to volume and page number in other Modules.

This QOS normally should not exceed 40 pages of text, excluding tables and figures. For biotech products and products manufactured using more complex processes, the document could be longer but normally should not exceed 80 pages of text (excluding tables and figures).

2.3.1 OVERVIEW OF THE ACTIVE PHARMACEUTICAL INGREDIENT(S) [API(S)]/DRUG SUBSTANCE

2.3.1.1 General Information
Summary Information from 3.2.1.1 should be included.

2.3.1.2 Manufacture
Information from 3.2.1.2 should be included:

- Summary Information on the manufacturer;
- A brief description of the manufacturing process (including, for example, reference to starting materials, critical steps, and reprocessing) and the controls that are intended to result in the routine and consistent production of material(s) of appropriate quality;
- *A flow diagram, as provided in 3.2.1.2.2;*
- A description of the Source and Starting Material and raw materials of biological origin used in the manufacture of the drug substance, as described in 3.2.1.2.3;
- A discussion of the selection and justification of critical manufacturing steps, process controls, and acceptance criteria. Highlight critical process intermediates, as described in 3.2.1.2.4;
- A description of process validation and/or evaluation, as described in 3.2.1.2.5.
- A brief summary of major manufacturing changes made throughout development and conclusions from the assessment used to evaluate product consistency, as described in 3.2.1.2.6. The QOS should also cross-refer to the non-clinical and clinical studies that used batches affected by these manufacturing changes, as provided in the Module 4 and 5 of the dossier.

2.3.1.3 Characterisation

For CE:

A summary of the interpretation of evidence of structure and isomerism, as described in 3.2.1.3.1, should be included.

When a drug substance is chiral, it should be specified whether specific stereoisomers or a mixture of stereoisomers have been used in the nonclinical and clinical studies, and information should be given as to the stereoisomer of the drug substance that is to be used in the final product intended for marketing.

For Biotech:

A description of the desired product and product-related substances and a summary of general properties, characteristic features and characterisation data (for example, primary and higher order structure and biological activity), as described in 3.2.1.3.1, should be included.

For CE and Biotech:

The QOS should summarise the data on potential and actual impurities arising from the synthesis, manufacture and/or degradation, and should summarise the basis for setting the acceptance criteria for individual and total impurities. The QOS should also summarise the impurity levels in batches of the drug substance used in the non-clinical studies, in the clinical trials, and in typical batches manufactured by the proposed commercial process. The QOS should state how the proposed impurity limits are qualified.

A tabulated summary of the data provided in 3.2.1.3.2, with graphical representation, where appropriate should be included.

2.3.1.4 Control of Drug Substance

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

Specification from 3.2.1.4.1 should be provided.

A tabulated summary of the batch analyses from 3.2.1.4.4, with graphical representation where appropriate, should be provided.

2.3.1.5 Reference Standards or Materials

Summary Information from 3.2.1.5 (tabulated presentation, where appropriate) should be included.

2.3.1.6 Container Closure System

A brief description and discussion of the information, from 3.2.1.6 should be included.

2.3.1.7 Stability

This section should include a summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions, the proposed storage conditions, retest date or shelf-life, where relevant, as described in 3.2.1.7.1.

The post-approval stability protocol, as described in 3.2.1.7.2, should be included.

A tabulated summary of the stability results from 3.2.1.7.3, with graphical representation where appropriate, should be provided.

2.3.2 OVERVIEW OF THE FINISHED PHARMACEUTICAL PRODUCT/DRUG PRODUCT

2.3.2.1 Description and Composition of the Drug Product

Summary Information from 3.2.2.1 should be provided.

Composition from 3.2.2.1 should be provided.

2.3.2.2 Pharmaceutical Development

A discussion of the information and data from 3.2.2.2 should be presented.

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

2.3.2.3 Manufacture

Information from 3.2.2.3 should include:

- Information on the manufacturer.

- A brief description of the manufacturing process and the controls that are intended to result in the routine and consistent production of product of appropriate quality.
- *A flow diagram, as provided under 3.2.2.3.3.*
- A brief description of the process validation and/or evaluation, as described in 3.2.2.3.5.

2.3.2.4 Control of Excipients
A brief summary on the quality of excipients, as described in 3.2.2.4, should be included.

2.3.2.5 Control of Drug Product
A brief summary of the justification of the specification(s), a summary of the analytical procedures and validation, and characterisation of impurities should be provided.

Specification(s) from 3.2.2.5.1 should be provided.

A tabulated summary of the batch analyses provided under 3.2.2.5.4, with graphical representation where appropriate should be included.

2.3.2.6 Reference Standards or Materials

Information from 3.2.5.6 (tabulated presentation, where appropriate) should be included.

2.3.2.7 Container Closure System
A brief description and discussion of the information in 3.2.2.7 should be included.

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

A tabulated summary of the stability results from 3.2.2.8.3, with graphical representation where appropriate, should be included.

The post-approval stability protocol, as described in 3.2.2.8.2, should be provided.

2.4 OVERVIEW AND SUMMARY OF NON CLINICAL AND CLINICAL DOCUMENTATION

General Principles of Nonclinical Overview and Summaries

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.

2.4.1 NEW CHEMICAL ENTITIES ONLY

2.4.1.1.1 NONCLINICAL OVERVIEW

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.

General Aspects

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

Except for biotechnology-derived products, an assessment of the impurities and degradants present in the drug substance and product should be included along with what is known of their potential pharmacologic and toxicologic effects. This assessment should form part of the justification for proposed impurity limits in the drug substance and product, and be appropriately cross-referenced to the quality documentation. The implications of any differences in the chirality, chemical form, and impurity profile between the compound

used in the nonclinical studies and the product to be marketed should be discussed. For biotechnology-derived products, comparability of material used in nonclinical studies, clinical studies, and proposed for marketing should be assessed. If a drug product includes a novel excipient, an assessment of the information regarding its safety should be provided.

Relevant scientific literature and the properties of related products should be taken into account. If detailed references to published scientific literature are to be used in place of studies conducted by the applicant, this should be supported by an appropriate justification that reviews the design of the studies and any deviations from available guideline. In addition, the availability of information on the quality of batches of drug substance used in these referenced studies should be discussed.

The Nonclinical Overview should contain appropriate reference citations to the Tabulated Summaries.

2.4.1.1.2 Content and Structural Format

The Nonclinical Overview should be presented in the following sequence:

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

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

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

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

- pharmacodynamics
- toxic signs
- causes of death
- pathologic findings
- genotoxic activity - the chemical structure of the compound, its mode of action, and its relationship to known genotoxic compounds
- carcinogenic potential in the context of the chemical structure of the compound, its relationship to known carcinogens, its genotoxic potential, and the exposure data
- the carcinogenic risk to humans - if epidemiologic data are available, they should be taken into account
- fertility, embryofetal development, pre-and post-natal toxicity
- studies in juvenile animals
- the consequences of use before and during pregnancy, during lactation, and during pediatric development
- local tolerance
- other toxicity studies/ studies to clarify special problems

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

- animal species used
- numbers of animals used
- routes of administration employed
- dosages used
- duration of treatment or of the study
- systemic exposures in the toxicology species at no observed adverse effect levels and at toxic doses, in relation to the exposures in humans at the maximum recommended human dose. Tables or figures summarising this information are recommended.
- the effect of the drug substance observed in nonclinical studies in relation to that expected or observed in humans

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

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

2.4.1.2 NONCLINICAL WRITTEN AND TABULATED SUMMARIES

2.4.1.2.1 Nonclinical Written Summaries

2.4.1.2.1.1 Introduction

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:

- Mouse
- Rat
- Hamster
- Other rodent
- Rabbit
- Dog
- Non-human primate
- Other non-rodent mammal

- Non-mammals

Routes of administration should be ordered as follows :

- The intended route for human use
- Oral
- Intravenous
- Intramuscular
- Intraperitoneal
- Subcutaneous
- Inhalation
- Topical
- Other

Use of Tables and Figures

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

To allow authors flexibility in defining the optimal structure for the Written Summaries, tables and figures should preferably be included within the text. 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:

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

2.4.1.2.2 Content of Nonclinical Written and Tabulated Summaries

2.4.1.2.2.1 Introduction

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

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

2.4.1.2.2.2 Pharmacology Written Summary

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

- Brief Summary
- Primary Pharmacodynamics
- Secondary Pharmacodynamics
- Safety Pharmacology
- Pharmacodynamic Drug Interactions
- Discussion and Conclusions
- Tables and Figures (either here or included in text)

2.4.1.2.2.2.1 *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).

2.4.1.2.2.2.2 *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.

2.4.1.2.2.2.3 *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.

2.4.1.2.2.2.4 *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.

2.4.1.2.2.2.5 *Pharmacodynamic Drug Interactions*

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

2.4.1.2.2.2.6 *Discussion and Conclusions*

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

2.4.1.2.2.2.7 *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.

2.4.1.2.2.3 Pharmacology Tabulated Summary

2.4.1.2.2.3.1 Pharmacokinetics Written Summary

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

- Brief Summary
- Methods of Analysis
- Absorption
- Distribution
- Metabolism
- Excretion
- Pharmacokinetic Drug Interactions

- Other Pharmacokinetic Studies
- Discussion and Conclusions
- Tables and Figures (either here or included in text)

2.4.1.2.2.3.1.1 *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.

2.4.1.2.2.3.2 *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.

2.4.1.2.2.3.3 *Absorption*

The following data should be summarised in this section:

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

2.4.1.2.2.3.4 *Distribution*

The following data should be summarised in this section:

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

2.4.1.2.2.3.5 *Metabolism (interspecies comparison)*

The following data should be summarised in this section:

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

2.4.1.2.2.3.6 *Excretion*

The following data should be summarised in this section:

- Routes and extent of excretion
- Excretion in milk

2.4.1.2.2.3.7 *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.

2.4.1.2.2.3.8 *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.

2.4.1.2.2.3.9 *Discussion and Conclusions*

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

2.4.1.2.2.3.10 *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.

2.4.1.2.2.4 Pharmacokinetics Tabulated Summary

2.4.1.2.2.4.1 Toxicology Written Summary

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

- Brief Summary
- Single-Dose Toxicity
- Repeat-Dose Toxicity
- Genotoxicity
- Carcinogenicity
- Reproductive and Developmental Toxicity
- Studies in Juvenile Animals
- Local Tolerance
- Other Toxicity Studies
- Discussion and Conclusions
- Tables and Figures (either here or included in text)

Brief Summary

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

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

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

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

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.

Other Toxicity Studies (if available)

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

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

Discussion and Conclusions

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

Tables and Figures

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

2.4.1.2.2.5 Toxicology Tabulated Summary

2.4.1.2.2.5.1 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.

2.4.1.3 CLINICAL OVERVIEW

Preamble

The Clinical Overview is intended to provide a critical analysis of the clinical data in the application. The Clinical Overview will necessarily refer to application data provided in the comprehensive Clinical Summary, the individual clinical study reports (ICH E3), and other relevant reports; but it should primarily present the conclusions and implications of those data, and should not recapitulate them. Specifically, the Clinical Summary should provide a detailed factual summarisation of the clinical information in the dossier, and the Clinical Overview should provide a succinct discussion and interpretation of these findings together with any other relevant information (e.g., pertinent animal data or product quality issues that may have clinical implications).

The Clinical Overview is primarily intended for use by regulatory agencies in the review of the clinical section of a marketing application. It should also be a useful reference to the overall clinical findings for regulatory agency staff involved in the review of other sections of the marketing application. The Clinical

Overview should present the strengths and limitations of the development program and study results, analyse the benefits and risks of the medicinal product in its intended use, and describe how the study results support critical parts of the prescribing information.

In order to achieve these objectives the Clinical Overview should:

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

The Clinical Overview should generally be a relatively short document (about 30 pages). The length, however, will depend on the complexity of the application. The use of graphs and concise tables in the body of the text is encouraged for brevity and to facilitate understanding. It is not intended that material presented fully elsewhere be repeated in the Clinical Overview; cross-referencing to more detailed presentations provided in the Clinical Summary or in Module 5 is encouraged.

2.4.1.3.1 Product Development Rationale

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

- identify the pharmacological class of the medicinal product.
- describe the particular clinical/pathophysiological condition that the medicinal product is intended to treat, prevent, or diagnose (the targeted indication).
- briefly summarise the scientific background that supported the investigation of the medicinal product for the indication(s) that was (were) studied.
- briefly describe the clinical development programme of the medicinal product, including ongoing and planned clinical studies and the basis for the decision to submit the application at this point in the programme. Briefly describe plans for the use of foreign clinical data (ICH E5).
- 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.

2.4.1.3.2 Overview of Biopharmaceutics

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

2.4.1.3.3 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:

- pharmacokinetics, e.g., comparative PK in healthy subjects, patients, and special populations; PK related to intrinsic factors (e.g., age, sex, race, renal and hepatic impairment) and to extrinsic factors (e.g., smoking, concomitant drugs, diet); rate and extent of absorption; distribution, including binding with plasma proteins; specific metabolic pathways, including effects of possible genetic polymorphism and the formation of active and inactive metabolites; excretion; time-dependent changes in pharmacokinetics; stereochemistry issues; clinically relevant PK interactions with other medicinal products or other substances.
- pharmacodynamics, e.g., information on mechanism of action, such as receptor binding; onset and/or offset of action; relationship of favorable and unfavorable pharmacodynamic effects to dose or plasma concentration (i.e., PK/PD relationships); PD support for the proposed dose and dosing interval; clinically relevant PD interactions with other medicinal products or substances; and possible genetic differences in response.
- interpretation of the results and implications of immunogenicity studies, clinical microbiology studies, or other drug class specific PD studies summarised in section 2.7.2.4 of the Clinical Summary.

2.4.1.3.4 Overview of Efficacy

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

The following issues should generally be considered:

- relevant features of the patient populations, including demographic features, disease stage, any other potentially important covariates, any important patient populations excluded from critical studies, and participation of children and elderly (ICH E11 and E7). Differences between the studied population(s) and the population that would be expected to receive the medicinal product after marketing should be discussed.
- implications of the study design(s), including selection of patients, duration of studies and choice of endpoints and control group(s). Particular attention should be given to endpoints for which there is limited experience. Use of surrogate endpoints should be justified. Validation of any scales used should be discussed.
- for non-inferiority trials used to demonstrate efficacy, the evidence supporting a determination that the trial had assay sensitivity and justifying the choice of non-inferiority margin (ICH E10).
- statistical methods and any issues that could affect the interpretation of the study results (e.g., important modifications to the study design, including endpoint assessments and planned analyses, as they were specified in the original protocol;
- support for any unplanned analyses; procedures for handling missing data; and corrections for multiple endpoints).
- similarities and differences in results among studies, or in different patient sub-groups within studies, and their effect upon the interpretation of the efficacy data.
- observed relationships between efficacy, dose, and dosage regimen for each indication, in both the overall population and in the different patient subgroups (ICH E4).
- support for the applicability to the new region of data generated in another region, where appropriate (ICH E5).
- for products intended for long-term use, efficacy findings pertinent to the maintenance of long-term efficacy and the establishment of long-term dosage. Development of tolerance should be considered.
- data suggesting that treatment results can be improved through plasma concentration monitoring, if any, and documentation for an optimal plasma concentration range.

- the clinical relevance of the magnitude of the observed effects.
- if surrogate endpoints are relied upon, the nature and magnitude of expected clinical benefit and the basis for these expectations.
- efficacy in special populations. If efficacy is claimed with inadequate clinical data in the population, support should be provided for extrapolating efficacy from effects in the general population.

2.4.1.3.5 Overview of Safety

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

- adverse effects characteristic of the pharmacological class. Approaches taken to monitor for similar effects should be described.
- special approaches to monitoring for particular adverse events (e.g., ophthalmic, QT interval prolongation).
- relevant animal toxicology and product quality information. Findings that affect or could affect the evaluation of safety in clinical use should be considered.
- the nature of the patient population and the extent of exposure, both for test drug and control treatments. Limitations of the safety database, e.g., related to inclusion/exclusion criteria and study subject demographics, should be considered, and the implications of such limitations with respect to predicting the safety of the product in the marketplace should be explicitly discussed.
- common and non-serious adverse events, with reference to the tabular presentations of events with the test drug and with control agents in the Clinical Summary. The discussion should be brief, focusing on events of relatively high frequency, those with an incidence higher than placebo, and those that are known to occur in active controls or other members of the therapeutic class. Events that are substantially more or less common or problematic (considering the duration and degree of the observed events) with the test drug than with active controls are of particular interest.
- serious adverse events (relevant tabulations should be cross-referenced from the Clinical Summary). This section should discuss the absolute number and frequency of serious adverse events, including deaths, and other significant adverse events (e.g., events leading to discontinuation or dose modification), and should discuss the results obtained for test drug versus control treatments. Any conclusions regarding causal relationship (or lack of this) to the product should be provided. Laboratory findings reflecting actual or possible serious medical effects should be considered.
- similarities and differences in results among studies, and their effect upon the interpretation of the safety data.
- any differences in rates of adverse events in population subgroups, such as those defined by demographic factors, weight, concomitant illness, concomitant therapy, or polymorphic metabolism.
- relation of adverse events to dose, dose regimen, and treatment duration.
- long-term safety (E1a).
- methods to prevent, mitigate, or manage adverse events.
- reactions due to overdose; the potential for dependence, rebound phenomena and abuse, or lack of data on these issues.
- world-wide marketing experience. The following should be briefly discussed: - the extent of the world-wide experience,
    - any new or different safety issues identified,
    - any regulatory actions related to safety.
- support for the applicability to the new region of data generated in another region, where appropriate (ICH E5).

2.4.1.3.6 Benefits and Risks Conclusions

The purpose of this section is to integrate all of the conclusions reached in the previous sections about the biopharmaceutics, clinical pharmacology, efficacy and safety of the medicinal product and to provide an overall appraisal of the benefits and risks of its use in clinical practice. Also, implications of any deviations

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

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

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

2.4.1.3.7 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.

*Reference: The first edition of the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* was conceived by the Vancouver Group and was published in 1979.

2.4.1.4 CLINICAL SUMMARY

Preamble

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 meta-analyses or other cross-study analyses for which full reports have been included in Module 5; and post-marketing data for products that have been marketed in other regions. 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.

2.4.1.4.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

2.4.1.4.1.1 *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.

2.4.1.4.1.2 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.

2.4.1.4.1.3 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:

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

2.4.1.4.2 Summary of Clinical Pharmacology Studies

2.4.1.4.2.1 *Background and Overview*

This section should provide the reviewer with an overall view of the clinical pharmacology studies. These studies include clinical studies performed to evaluate human pharmacokinetics (PK), and pharmacodynamics (PD), and *in vitro* studies performed with human cells, tissues, or related materials (hereinafter referred to as human biomaterials) that are pertinent to PK processes. For vaccine products, this section should provide the reviewer with immune response data that support the selection of dose, dosage schedule, and formulation of

the final product. Where appropriate, relevant data that are summarised in sections 2.4.1.4.1, 2.4.1.4.3 and 2.4.1.4.4 can also be referenced to provide a comprehensive view of the approach and rationale for the development of the pharmacokinetic, pharmacodynamic, PK/PD and human biomaterial database. This section should not include detailed information about individual studies.

This section should begin with a brief overview of the human biomaterial studies that were conducted and that were intended to help in the interpretation of PK or PD data. Studies of permeability (e.g., intestinal absorption, blood brain barrier passage), protein binding, hepatic metabolism, and metabolic-based drug-drug interactions are particularly relevant. This should be followed by a brief overview of the clinical studies that were carried out to characterise PK and PD of the medicinal product, including studies of PK/PD relationships in healthy subjects and patients, and relevant effects of intrinsic and extrinsic factors on PK and PK/PD relationships2. Critical aspects of study design and data analysis should be noted, e.g., the choice of the single or multiple doses used, the study population, choice of the intrinsic or extrinsic factors that were studied, the choice of PD endpoints, and whether a traditional approach or a population approach was used to collect and analyse data to assess PK or PD.

2.4.1.4.2.2 Summary of Results of Individual Studies

A tabular listing of all clinical pharmacology studies should generally be provided (see 2.7.2.5 Appendix), together with a narrative description of the relevant features and outcomes of each of the critical individual studies that provided *in vitro* or *in vivo* data and information relevant to PK, PD and PK/PD relationships. The narrative descriptions should be brief, e.g., similar to an abstract for a journal article, and should describe critical design features and critical results. Similar studies may be described together, noting the individual study results and any important differences among the studies. References or electronic links to the full report of each study should be included in the narratives.

Summaries of dose-response or concentration response (PK/PD) studies with pharmacodynamic endpoints should generally be included in this section. In some cases, however, when well-controlled dose-response PD or PK/PD studies provide important evidence of efficacy or safety, they should be placed in 2.4.1.4.3 or 2.4.1.4.4 as appropriate and referenced, but not summarised, here.

2.4.1.4.2.3 Comparison and Analyses of Results Across Studies

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

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

- *in vitro* drug metabolism and *in vitro* drug-drug interaction studies and their clinical implications.
- human PK studies, including the best estimates of standard parameters and sources of variability. The focus should be on evidence supporting dose and dose individualisation in the target patient population and in special populations, e.g., paediatric or geriatric patients, or patients with renal or hepatic impairment.
- comparison between single and repeated-dose PK
- population PK analyses, such as results based on sparse sampling across studies that address inter-individual variations in the PK or PD of the active drug substances that may be due to extrinsic or intrinsic factors.
- dose-response or concentration-response relationships. This discussion should highlight evidence to support the selection of dosages and dose intervals studied in the important clinical trials. In addition, information that supports the dosage instructions in the proposed labelling should be discussed in Section 2.7.3.4.
- major inconsistencies in the human biomaterial, PK, or PD database.
- PK studies that were performed to determine whether foreign clinical data could be extrapolated to the new region (see ICH E5). The result of the studies and analysis of the similarity of the PK data between regions or races should be summarised in this section. Such studies that use PD biomarkers (but do not evaluate clinical efficacy) may similarly be summarised here. An independent subsection can be created to summarise these kinds of data.

2.4.1.4.2.4 Special Studies

This section should include studies that provide special types of data relevant to specific types of medicinal products. For immunogenicity studies and other studies in which data may correlate with PK, PD, safety, and/or efficacy data, explanations of such correlations should be summarised here. Any observed or potential effects on PK, PD, safety and/or efficacy should be considered in other appropriate sections of the Clinical Summary as well, with cross-referencing to this section. Human studies that address a specific safety issue should not be reported here, but instead should be reported in the Summary of Clinical Safety (section 2.4.1.4.4).

Example 1: Immunogenicity

For protein products and other products to which specific immunological reactions have been measured, data regarding immunogenicity should be summarised in this section. For vaccines or other products intended to induce specific immune reactions, immunogenicity data should be described in the efficacy section 2.4.1.4.3. Assays used should be briefly described and information about their performance (e.g., sensitivity, specificity, reliability, validity) should be summarised; the location in the application of detailed information should be cross-referenced.

Data regarding the incidence, titre, timing of onset and duration of antibody responses should be summarised for each type of antibody assay used (e.g., IgG by ELISA, neutralisation). Relationships of antibody formation to underlying disease, concomitant medication, dose, duration, regimen, and formulation should be explored and summarised. For drugs intended to be given as chronic, continuous therapy, any data on the impact of interruptions of therapy on antigenicity should be analysed and summarised.

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

Example 2: Clinical microbiology

For antimicrobial or antiviral medicinal products, *in vitro* studies to characterise the spectrum of activity are an important part of the programme of studies relevant to clinical efficacy. Clinical efficacy studies that include characterisation of the susceptibility of the clinical isolates as a part of the efficacy determination should be included in Section 2.4.1.4.3, Summary of Clinical Efficacy. However, studies that evaluate such findings as the pattern of *in vitro* susceptibility of strains of bacteria from different parts of the world (not in the context of clinical efficacy study) would be included here.

2.4.1.4.3 Summary of Clinical Efficacy

A separate Section 2.4.1.4.3 should be provided for each indication, although closely related indications can be considered together. When more than one Section 2.4.1.4.3 is submitted, the sections should be labelled 2. 4.1.4.3 pneumonia, 2. 4.1.4.3 URI, etc.

2.4.1.4.3.1 Background and Overview of Clinical Efficacy

This section should describe the program of controlled studies and other pertinent studies in the application that evaluated efficacy specific to the indication(s) sought. Any results of these studies that are pertinent to evaluation of safety should be discussed in Section 2. 4.1.4.4, Summary of Clinical Safety.

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

2.4.1.4.3.2 Summary of Results of Individual Studies

A tabular listing of all studies that provided (or were designed to provide) information relevant to product efficacy should generally be provided (see the section 2. 4.1.4.3.6 Appendix), together with narrative descriptions for important studies. The narrative descriptions should be brief, e.g., similar to an abstract for a journal article, and should describe critical design features and critical results. Similar studies may be

described together, noting the individual study results and any important differences among the studies. For studies that also contributed significantly to the safety analysis, study narratives should include information about the extent of exposure of study subjects to the test drug or control agent, and how safety data were collected. These narratives can be abstracted from the synopses of the clinical study reports (ICH E3). References or electronic links to the full report of each study should be included in the narratives.

Narratives of any bridging studies using clinical endpoints, i.e., certain studies intended to evaluate the ability to extrapolate certain types of foreign clinical data to the new region (see ICH E5), should be included in this section. An analysis of the results of such studies, together with other information (e.g., PK and PD data) that addresses the ability to extrapolate the efficacy and safety results of foreign studies, should be performed if necessary. The conclusions of such an analysis should be noted at the start of Section 2.4.1.4.3.3.2, Comparison of Efficacy Results of All Studies, and the full report of the analysis should be provided in Module 5.

2.4.1.4.3.3 Comparison and Analyses of Results Across Studies

Using text, figures, and tables as appropriate (see the section 2.4.1.4.3.6 Appendix), the subsections of 2.4.1.4.3.3 should summarise all available data that characterise the efficacy of the drug. This summary should include analyses of all data, irrespective of their

support for the overall conclusion and should, therefore, discuss the extent to which the results of the relevant studies do or do not reinforce each other. Any major inconsistencies in the data regarding efficacy should be addressed and any areas needing further exploration should be identified.

The section will generally utilise two kinds of analyses: comparison of results of individual studies, and analysis of data combined from various studies. Details of analyses that are too extensive to be reported in a summary document should be presented in a separate report, to be placed in Module 5.

This section should also cross-reference important evidence from section 2.4.1.4.2, such as data that support the dosage and administration section of the labelling. These data include dosage and dose interval recommended, evidence pertinent to individualisation of dosage and need for modifications of dosage for specific subgroups (e.g., paediatric or geriatric subjects, or subjects with hepatic or renal impairment), and data relevant to dose-response or concentration response (PK/PD) relationships.

Study Populations

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

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

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

Comparison of Efficacy Results of all Studies

The results of any bridging studies using clinical endpoints, i.e., certain studies used to evaluate the ability to extrapolate certain types of foreign clinical data to the new region (see ICH E5), should be summarised in this section. An analysis of the similarity of efficacy in subjects between regions, as well as any other information that may support extrapolation of the efficacy data to the new region, should be summarised here. An independent subsection can be created to summarize these kinds of data.

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

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

time are important, results of studies may be displayed in a figure that illustrates the change over time in each study.

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

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

If a meta-analysis of the clinical studies is performed, it should be clear whether this analysis is conducted according to a predefined protocol or is a post hoc exercise. Any differences in trial designs or populations, or in efficacy measurements between trials should be described to allow assessment of the relevance and validity of the results and conclusions (See ICH E9). A detailed description of the methodology and results of the meta-analysis should generally be submitted in a separate report (Module 5).

Comparison of Results in Sub-populations

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

Given the limited sample sizes in individual studies, analyses across multiple studies should be performed to evaluate effects of major demographic factors (age, sex, and race) and of other predefined or relevant intrinsic and extrinsic factors (e.g., disease severity, prior treatment, concomitant illness, concomitant drugs, alcohol, tobacco, and body weight) on efficacy. Factors of special interest may arise from general concerns (e.g., the elderly) or from specific issues that are related to the pharmacology of the drug or that have arisen during earlier drug development. Efficacy in the paediatric population should be routinely analysed in applications for a proposed indication that occurs in children. Depending on the data set, if extensive, detailed efficacy analyses are performed, they can be placed in Module 5, with the results of those analyses reported here.

2.4.1.4.3.4 Analysis of Clinical Information Relevant to Dosing Recommendations

This section should provide an integrated summary and analysis of all data that pertain to the dose-response or blood level-response relationships of effectiveness (including dose-blood level relationships), and thus have contributed to dose selection and choice of dose interval. Relevant data from nonclinical studies may be referenced, and relevant data from pharmacokinetic studies, other clinical pharmacology studies, and controlled and uncontrolled clinical studies should be summarised to illustrate these dose-response or blood level-response relationships. For pharmacokinetic and pharmacodynamics

studies from which data have been summarised in Section 2.4.1.4.2.2, it may be appropriate to draw upon those data in this summary while cross-referencing the summaries in Section 2.4.1.4.2.2, without repeating those summaries.

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

Any evidence of differences in dose-response relationships that result from a patient's age, sex, race, disease, or other factors should be described. Any evidence of different pharmacokinetic or pharmacodynamic responses should also be discussed, or discussions in Section 2.4.1.4.2 can be cross-referenced. The ways in which such differences were looked for, even if no differences were found, should be described (e.g., specific studies in subpopulations, analysis of efficacy results by subgroup, or blood level determinations of the test drug).

2.4.1.4.3.5 *Persistence of Efficacy and/or Tolerance Effects*

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

The primary focus should be on controlled studies specifically designed to collect long-term efficacy data, and such studies should be clearly differentiated from other, less rigorous, studies such as open extension studies. This distinction also applies to specific studies designed for evaluation of tolerance and withdrawal effects. Data concerning withdrawal or rebound effects pertinent to product safety should be presented in the safety section (see section 2.4.1.4.4).

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

2.4.1.4.4 Summary of Clinical Safety

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

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

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

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

2.4.2 GENERIC DRUG APPLICATIONS ONLY

2.4.2.1 CLINICAL OVERVIEW AND CLINICAL SUMMARY

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

The Clinical Overview is primarily intended for use by regulatory agencies in the review of the clinical section of a marketing application. It should also be a useful reference to the overall clinical findings for regulatory agency staff involved in the review of other sections of the marketing application. The Clinical Overview should present the strengths and limitations of the development program and study results, analyse the benefits and risks of the medicinal product in its intended use, and describe how the study results support critical parts of the prescribing information.

In order to achieve these objectives the Clinical Overview should:

- describe and explain the overall approach to the clinical development of a medicinal product, including critical study design decisions.
- assess the quality of the design and performance of the studies, and include a statement regarding GCP compliance.

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

The Clinical Overview should generally be a relatively short document (about 30 pages). The length, however, will depend on the complexity of the application. The use of graphs and concise tables in the body of the text is encouraged for brevity and to facilitate understanding. It is not intended that material presented fully elsewhere be repeated in the Clinical Overview; cross-referencing to more detailed presentations provided in the Clinical Summary or in Module 5 is encouraged.

2.4.2.1.1 Product Development Rationale

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

- identify the pharmacological class of the medicinal product.
- describe the particular clinical/pathophysiological condition that the medicinal product is intended to treat, prevent, or diagnose (the targeted indication).
- briefly summarise the scientific background that supported the investigation of the medicinal product for the indication(s) that was (were) studied.
- briefly describe the clinical development programme of the medicinal product, including ongoing and planned clinical studies and the basis for the decision to submit the application at this point in the programme. Briefly describe plans for the use of foreign clinical data (ICH E5).
- 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.

2.4.2.1.2 Overview of Biopharmaceutics studies

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).

2.4.2.1.3 Summary of Biopharmaceutic Studies and Associated Analytical Methods

2.4.2.1.3.1 *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.

2.4.2.1.3.2 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.

2.4.2.1.3.3 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:

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

2.4.2.1.4 Overview and summary of *In vitro* dissolution tests complementary to bioequivalence studies

Provide a brief overview and summary of 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 reference 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.

2.4.2.1.5 Overview and summary *In vitro* dissolution tests in support of biowaiver of strengths

Provide an overview and summary to justify for waiving of bioequivalence testing.

MODULE 3: CHEMICAL-PHARMACEUTICAL DOCUMENTATION

This part is intended to provide guidance on the format of a registration application for drug substances and their corresponding drug products as defined in the scope of the ICH Guidelines Q 6 A ("NCE") and ICH Guideline Q 6 B ("Biotech"). This format may also be appropriate for certain other categories of products though it has been modified to suit Generic drug applications.

3.1 TABLE OF CONTENTS OF MODULE 3

A Table of Contents for the filed application should be provided.

3.2 BODY OF DATA

The "Body of Data" in this guideline merely indicates where the information should be located. Neither the type nor extent of specific supporting data has been addressed in this guideline.

3.2.1 PARTICULARS OF ACTIVE PHARMACEUTICAL INGREDIENT(s) [API(s)]/ DRUG SUBSTANCE

The information on the API can be submitted according to the following order of preference:

- Provide the latest, valid European Certificate of Suitability (CEP) with all appendices. The information, which may not be covered by the CEP, should be provided under points 3.2.1.1.3.2, 3.2.1.5.2, 3.2.1.6 and 3.2.1.7.
- Provide a Drug Master File(s) [DMF(s)] submitted by the API manufacturer, provided that the DMF contains all the information listed under **Section 3.2.1**, or
- By completing **Section 3.2.1**. In this case, the API manufacturer should provide a signed declaration that the synthesis and subsequent purification is conducted in accordance with what is presented in the dossier.
- For a drug product containing more than one drug substance, the information requested for "module labelled Particulars of Active Pharmaceutical Ingredient(S) [API(s)]/ Drug Substance" should be provided in its entirety for each drug substance

3.2.1.1 General Information

3.2.1.1.1 Nomenclature

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

- Recommended International Nonproprietary Name (INN);
- Compendial name if relevant;
- Chemical name(s);
- Company or laboratory code;
- Other non-proprietary name(s), e.g., national name, United States Adopted Name (USAN), Japanese Accepted Name (JAN); British Approved Name (BAN), and
- Chemical Abstracts Service (CAS) registry number.

3.2.1.1.2 Structure

CE:

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

Biotech:

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

3.2.1.1.3 General Properties of the API(s)

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

Reference ICH Guidelines: Q6A and Q6B

3.2.1.1.3.1 API not described in BP, PhInt, JP, PhEur or USP

Provide the following information:

a) Chemical structure, including relative and absolute stereochemistry, the molecular formula and the relative molecular mass;

b) Isomeric nature including stereochemical configuration;

c) Documented evidence of structure and stereochemistry, such as clearly visible, Quality Assurance (QA)-certified copies of infrared, nuclear magnetic resonance (proton and C-13), ultraviolet and mass spectra, together with professional interpretation of the relevant parts of spectra, X-ray diffractograms, thermograms, and so on;

d) Physicochemical and other relevant properties of the API, such as solubility in water, other solvents such as ether, ethanol, acetone, and buffers of different pH; partition coefficient; existence/absence of polymorphs and water/solvent of crystallization; results of hygroscopicity testing; particle size and so on.

3.2.1.1.3.2 API described in BP, PhInt, JP, PhEur, or USP

Identify physicochemical and other properties of the API, which are not included in a pharmacopoeial monograph and are relevant to product safety and efficacy, such as solubility in water, other solvents such as ether, ethanol, acetone, and buffers of different pH; partition coefficient; existence/absence of polymorphs and water/solvent of crystallization; results of hygroscopicity testing; particle size, and so on.

3.2.1.1.3.3 Information from literature

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

3.2.1.2 Manufacturer of API(s)

3.2.1.2.1 Name and address of API(s) Manufacturer

State the name and street address of each facility where manufacture (synthesis, production) of API occurs, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided. Provide phone number(s); fax number(s) and e-mail addresses. Include any alternative manufacturers.

Provide a valid Manufacturing Authorization for the production of APIs. If available, attach a certificate of GMP compliance.

Reference: *WHO pharmaceutical starting materials certification scheme (SMACS): guidelines on implementation (WHO Technical Report Series, No. 917, 2003)*

3.2.1.2.2 Description of Manufacturing Process and Process Controls (name, manufacturer)

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

CE:

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 drug substance 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 3.2.1.2.5.

3.2.1.2.2.1 Specifications of raw materials and intermediates used in the synthesis

Provide specifications for starting materials, reagents, solvents, catalysts, and intermediates (if isolated during the process) in the synthesis. Provide information demonstrating that materials meet standards appropriate for their intended use (including the clearance or control of adventitious agents), as appropriate.

3.2.1.2.2.2 API described in BP, PhInt, JP, PhEur, or USP

An outline of the route of synthesis should be provided (a simplified flow chart and a qualitative description of the manufacturing method, including the name of solvents, reagents and catalysts) with special emphasis on the final steps including purification procedures.

List process-related impurities not included in the monograph(s) (e.g., key intermediates, residual solvents), which can be identified from the simplified flow diagram and text-book level narrative of the synthetic process

Biotech:

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

Batch(es) and scale definition

An explanation of the batch numbering system, including information regarding any pooling of harvests or intermediates and batch size or scale should be provided.

Cell culture and harvest

A flow diagram should be provided that illustrates the manufacturing route from the original inoculum (e.g. cells contained in one or more vials(s) of the Working Cell Bank up to the last harvesting operation. The diagram should include all steps (i.e., unit operations) and intermediates. Relevant information for each stage, such as population doubling levels, cell concentration, volumes, pH, cultivation times, holding times, and temperature, should be included. Critical steps and critical intermediates for which specifications are established (as mentioned in 3.2.1.2.4) should be identified.

A description of each process step in the flow diagram should be provided. Information should be included on, for example, scale; culture media and other additives (details provided in 3.2.1.2.3); major equipment; and process controls, including in-process tests and operational parameters, process steps, equipment and intermediates with acceptance criteria (details provided in 3.2.1.2.4). Information on procedures used to transfer material between steps, equipment, areas, and buildings, as appropriate, and shipping and storage conditions should be provided. (Details on shipping and storage provided in 3.2.1.2.4.)

Purification and modification reactions

A flow diagram should be provided that illustrates the purification steps (i.e., unit operations) from the crude harvest(s) up to the step preceding filling of the drug substance. All steps and intermediates and relevant information for each stage (e.g., volumes, pH, critical processing time, holding times, temperatures and elution profiles and selection of fraction, storage of intermediate, if applicable) should be included. Critical steps for which specifications are established as mentioned in 3.2.1.2.4 should be identified.

A description of each process step (as identified in the flow diagram) should be provided. The description should include information on, for example, scale, buffers and other reagents (details provided in 3.2.1.2.3, major equipment, and materials. For materials such as membranes and chromatography resins, information for conditions of use and reuse also should be provided. The description should include process controls (including in-process tests and operational parameters) with acceptance criteria for process steps, equipment and intermediates. (Details in 3.2.1.2.4.)

Reprocessing procedures with criteria for reprocessing of any intermediate or the drug substance should be described. (Details should be given in 3.2.1.2.5.)

Information on procedures used to transfer material between steps, equipment, areas, and buildings, as appropriate, and shipping and storage conditions should be provided (details on shipping and storage provided in 3.2.1.2.4.).

Filling, storage and transportation (shipping)

A description of the filling procedure for the drug substance, process controls (including in-process tests and operational parameters), and acceptance criteria should be provided. (Details in 3.2.1.2.4.) The container closure system(s) used for storage of the drug substance (details in 3.2.1.6.) and storage and shipping conditions for the drug substance should be described.

Reference ICH Guidelines: Q5A, Q5B, and Q6B

3.2.1.2.3 Control of Materials

CE:

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

Reference ICH Guidelines: Q6A and Q6B

Biotech:

Control of Source and Starting Materials of Biological Origin

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

Source, history, and generation of the cell substrate

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

Cell banking system, characterisation, and testing

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

Reference ICH Guidelines: Q5A, Q5B, Q5C and Q5D

3.2.1.2.4 Controls of Critical Steps and Intermediates

Critical Steps: Tests and acceptance criteria (with justification including experimental data) performed at critical steps identified in 3.2.1.2.2 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.

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

Provide a flow diagram of the synthetic process (es) that includes molecular formulae, weights, yield ranges, chemical structures of starting materials, intermediates, reagents and API reflecting stereochemistry, and identifies operating conditions, purification steps, catalysts and solvents.

Submit a sequential procedural narrative of the manufacturing process. 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).

When the API is still to be produced in commercial quantities (pilot scale batches), it can be registered provided scale-up is immediately reported to PPB.

When the submitted route of synthesis consists of a limited number of steps (e.g., one to three), full details of the manufacture of the starting material(s) or key intermediates should be given and/or at least detailed specifications especially regarding the impurity profile including residual solvents and catalysts.

Reference ICH Guidelines: Q6A and Q6B

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

Reference ICH Guideline: Q5C

3.2.1.2.5 Process Validation and/or Evaluation

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

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

Process validation of critical steps of the synthesis and aseptic processing and sterilization, when applicable, should be included. The scale of manufacture / typical batch size should be stated.

A declaration on the use/non-use of material of animal or human origin should be provided.

Starting materials from vegetable origin should be fully characterized and a contaminant profile should be established and submitted.

Biotech:

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

The plan for conducting the study should be described and the results, analysis and conclusions from the executed study(ies) should be provided. The analytical procedures and corresponding validation should be cross-referenced (e.g., 3.2.1.2.4, 3.2.1.4.3) or provided as part of justifying the selection of critical process controls and acceptance criteria.

For manufacturing steps intended to remove or inactivate viral contaminants, the information from evaluation studies should be provided in 3.2.3.2.

3.2.1.2.6 Manufacturing Process Development

CE:

A description and discussion should be provided of the significant changes made to the manufacturing process and/or manufacturing site of the drug substance used in producing nonclinical, clinical, scale-up, pilot, and, if available, production scale batches.

Description and discussion of the significant changes made to the manufacturing process and/or manufacturing site of the API used in producing clinical, comparative, stability, scale-up, pilot, and, if available, production scale batches

Explain alternate processes and describe with the same level of detail as the primary process. It should be demonstrated that batches obtained by alternate processes have the same impurity profile as the principal process. If the obtained impurity profile is different, it should be demonstrated as to be acceptable according the requirements described further in the text for “impurities”.

Reprocessing steps should be identified and justified. Any data to support this justification should be either referenced or submitted.

Provide external environmental impact statement (aquatic, atmospheric and terrestrial environment, potential for harm, disposal sites and methods).

Reference should be made to the drug substance data provided in section 3.2.1.4.4.

Reference ICH Guideline: Q3A

Biotech:

The developmental history of the manufacturing process, as described in 3.2.1.2.2, should be provided. The description of change(s) made to the manufacture of drug substance batches used in support of the marketing application (e.g., nonclinical or clinical studies) should include, for example, changes to the process or to critical equipment. The reason for the change should be explained. Relevant information on drug substance batches manufactured during development, such as the batch number, manufacturing scale, and use (e.g., stability, nonclinical, reference material) in relation to the change, should be provided.

The significance of the change should be assessed by evaluating its potential to impact the quality of the drug substance (and/or intermediate, if appropriate). For manufacturing changes that are considered significant, data from comparative analytical testing on relevant drug substance batches should be provided to determine the impact on quality of the drug substance (see Q6B for additional guidance). A discussion of the data, including a justification for selection of the tests and assessment of results, should be included.

Testing used to assess the impact of manufacturing changes on the drug substance(s) and the corresponding drug product(s) can also include nonclinical and clinical studies. Cross-reference to the location of these studies in other modules of the submission should be included.

Reference should be made to the drug substance data provided in section 3.2.1.4.4.

Reference ICH Guideline: Q6B

3.2.1.3 Characterisation of API(s)

3.2.1.3.1 Elucidation of Structure and other Characteristics of the API(s)

CE:

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.

Reference ICH Guideline: Q6A

Biotech:

For desired product and product-related substances, details should be provided on primary, secondary and higher-order structure, post-translational forms (e.g., glycoforms), biological activity, purity, and immunochemical properties, when relevant.

Reference ICH Guideline: Q6B

3.2.1.3.2 Impurities

Information on impurities should be provided.

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

List of 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
		Potential impurity of the starting material(s)
		Unreacted starting material(s)
		Unreacted intermediate(s)
		By-product(s)
		Reagent(s)
		Catalyst(s)
		Residual solvent(s)
		Potential degradant(s)

Basis for setting the acceptance criteria for impurities:

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

Data on observed impurities for relevant FPP batches (e.g., clinical, comparative):

Impurity (API- and process-related)	Acceptance Criteria	Results [FPP batch number* and use (e.g., clinical, comparative)]		

* include strength, if reporting impurity levels found in the FPP (e.g., for comparative studies)

Justification of proposed acceptance criteria for impurities:

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

3.2.1.4 Control of Drug Substance

3.2.1.4.1 Specification of the drug substance

The specification for the drug substance should be provided.

3.2.1.4.1.1 API not described in BP, PhInt, JP, PhEur or USP

Provide justification for the API specification.

Reference*: ICH-Q6A — Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances + Decision trees*

Characterize and analyze synthesis impurities, including residual solvents, which may be present in API. Particular attention should be given to justifying cases where testing for possible impurities are omitted, e.g., due to the fact that the impurity has not been detected in any batches or will not potentially be present due to a particular method of production.

References:

- *Q3A(R) Impurities in New Drug Substances*
- *FDA (CDER) Guidance for Industry – ANDAs: Impurities in Drug Substances (Rev. 1, January 2005).*
- *Q3C Impurities: Guideline for Residual Solvents*
- *Q3C (M) Impurities: Residual Solvents (Maintenance) Permissible Daily Exposure (PDE) for Tetrahydrofuran and N. Methylpyrrolidine*

Provide analytical validation information, including experimental data for the analytical procedures used for testing the API and impurities. Include test methods in sufficient detail for them to be replicated by another laboratory.

References:

- *WHO Guideline: Validation of analytical procedures used in the examination of pharmaceutical materials.*
- *ICH-Q2A Text on Validation of Analytical Procedures*
- *ICH-Q2B Validation of Analytical Procedures: Methodology*
- *WHO Expert Committee on Specifications for Pharmaceutical Preparations. 32nd report. Geneva, WHO, 1992 (WHO Technical Report Series, No. 823) in "Quality assurance of pharmaceuticals – A compendium of guidelines and related materials." Volume 1. WHO, Geneva, pp. 119-124 (1997).*

Provide information on the preparation and studies to establish the identity, purity and assay value of in-house primary (absolute) and secondary (working) standards. Submit Certificate of Analysis (CoA) of in-house primary standards for use in assays, including:

- assay by two different validated methods,
- identification and control of impurities,
- storage instructions, and
- duration of use of the standards.

Reference: *ICH Q6A — Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances.*

Provide verified certificates of analysis for at least two batches produced at each site of manufacture by each synthetic method, including results for impurities.

3.2.1.4.1.2 API described in BP, PhInt, JP, PhEur or USP

Provide a copy of the monograph together with any test methods referenced in the monograph but not appearing in it. Note that the current monograph should always control the quality of the API.

The quality of the API should meet not only the requirements of specific monographs but also those described in the general monographs of a pharmacopoeia on APIs, excipients and other substance for pharmaceutical use.

Tests and limits should, as a minimum, comply with the relevant pharmacopoeial requirements. Whenever, an API has been prepared by a method liable to leave impurities not controlled in the pharmacopoeial monograph, these impurities (based on 3 to10 batch analysis results), including residual organic solvents, as well as their maximum tolerance limits should be declared and controlled by a suitable test procedure.

Provide details of any specifications for potentially critical quality variables (e.g. polymorphs, particle size, loss on drying, as identified during development chemistry) additional to those in the pharmacopoeia.

Provide verified certificates of analysis for at least two batches produced at each site of manufacture by each synthetic method, including results for impurities.

Reference ICH Guidelines: Q6A and Q6B

3.2.1.4.2 Analytical Procedures for testing the drug substance

The analytical procedures used for testing the drug substance should be provided.

Reference ICH Guidelines: Q2A and Q6B

3.2.1.4.3 Validation of Analytical Procedures

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

Reference ICH Guidelines: Q2A, Q2B, and Q6B

3.2.1.5 Reference Standards or Materials

Information on the reference standards or reference materials used for testing of the drug substance should be provided.

Reference ICH Guidelines: Q6A and Q6B

3.2.1.6 Container Closure System

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

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

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

3.2.1.7 Stability Testing of the API(s)

3.2.1.7.1 Stability Summary and Conclusions

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

3.2.1.7.2 Post-approval Stability Protocol and Stability Commitment

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

Reference ICH Guidelines: Q1A and Q5C

3.2.1.7.3 Stability Data

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

Reference ICH Guidelines: Q1A, Q1B, Q2A, Q2B, and Q5C

3.2.1.7.3.1 Stress testing (forced degradation)

Publications from peer-reviewed literature could be submitted to support/replace experimental data.
Stress testing of the API can help to identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual API and the type of FPP involved.

Degradation paths for pharmaceutical compounds are typically reactions of hydrolysis, oxidation, photolysis, and/or acid-base chemistry. To force these reactions, the API or FPP is placed in solution expediently, for example, under the conditions shown in the following table.

Stress factor	**Conditions**	**Concentration of API**	**Time**
Heat	60°C	1 x in diluent	1-10 days
Humidity	75% RH or greater	Solid state	1-10 days
Acid	0.1N HCl	2x	1-10 days
Base	0.1N NaOH	2x	1-10 days
Oxidative	3% H_2O_2	1x	1-3 days
Photolytic	Metal halide, Hg, Xe lamp, or UV-B/fluorescent	1x in diluent	1-10 days
Metal ions (optional)	0.05 M Fe2+ or Cu2+	1x in diluent	1-10 days

The objective is not to completely degrade the active compound but to generate degradation to a small extent, typically 10-30% loss of active by assay when compared with non-degraded compound. This target is chosen so that some degradation occurs, but it is not so severe that secondary products are generated. (Secondary degradation products are degradation products of degradation products and in most cases are not observed during stability studies.) In the total absence of degradation products after 10 days, the API is considered stable. If degradation is detectable but its extent is less than 10%, then the stress factors or the stress conditions, or both, should be increased.

Stress testing is to be carried out on a single batch of the API. Photostability testing should be an integral part of stress testing. The standard conditions for photostability testing are described in ICH Q1B.

Solid-state degradation can also be considered. For APIs, placing a solid sample at elevated temperatures — e.g., 60-120 °C, or 5-10 °C below the melting point— can generate some degradation compounds. Because of the harsher conditions, these compounds may not be observed under the accelerated stress studies. However, this approach serves to generate degradation products that can be used as a worst case to assess the analytical method performance.

Examining degradation products under stress conditions is also useful in developing and validating suitable analytical procedures. However, it may not be necessary to examine specifically for certain degradation

products if it has been demonstrated that they are not formed under accelerated or long term storage conditions. Results from these studies form an integral part of the information provided to PPB.

For APIs not described in an official pharmacopoeial monograph, there are two options:

- When available, it is acceptable to provide the relevant data published in the "peer review" literature to support the proposed degradation pathways.
- When no data are available in the scientific literature, including official pharmacopoeias, stress testing should be performed. Results from these studies will form an integral part of the information provided to PPB.

Reference: *ICH-Q1A (R2) Stability Testing of New Drug Substances and Products:*

3.2.1.7.3.2 Regulatory stability testing

Summarize the stability testing program and report the results of stability testing of not less than three (minimum one production scale and two pilot scale) batches of the API as described in **Annex II**. The data for each attribute should be discussed, trends analyzed and a re-test date should be proposed. Information on the analytical procedures used to generate the data and validation of these procedures should be included.

Describe the methodology used during stability studies; if this is identical to methodology described elsewhere in the dossier, a cross-reference will suffice. If different methodology was used, provide validation of tests for impurities including degradants and assay and for other tests as necessary.

At the time of submitting the dossier, the general requirements are:

Storage temperature (°C)	Relative humidity (%)	Minimum time period covered by data at submission (months)
Accelerated: 40±2	75±5	6
Long term: 30±2	65±5	12

Provide the post-approval stability protocol and stability-testing commitment, when applicable.

References:

- *Q1A (R2) Stability Testing of New Drug Substances and Products*
- *Q1B Stability Testing: Photostability Testing of New Drug Substances and Products*
- *Q1E Evaluation for Stability Data*
- *WHO list of stable APIs - Supplement 2.*

A storage statement should be proposed for the labelling (if applicable), which should be based on the stability evaluation of the API.

A re-test period should be derived from the stability information, and the approved re-test date should be displayed on the container label and CoA.

Unless otherwise justified, the long-term stability studies should be conducted at 30°C ± 2°C/75± 5%RH conditions.

Reference ICH Guidelines: Q1A, Q1B, and Q5C

3.2.2 PARTICULARS OF FINISHED PHARMACEUTICAL PRODUCT(s) [FPP(s)]/DRUG PRODUCT

3.2.2.1 Description and Composition of the Drug Product (name, dosage form)

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

Description of the dosage form;

- Composition, i.e., list of all components of the dosage form, and their amount on a per-unit basis (including overages, if any) the function of the components, and a reference to their quality standards (e.g., compendial monographs or manufacturer's specifications)
- Description of accompanying reconstitution diluent(s); and
- Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable.
- For a drug product supplied with reconstitution diluent(s), the information on the diluent(s) should be provided in a separate part "P", as appropriate

Reference ICH Guidelines: Q6A and Q6B

3.2.2.2 Pharmaceutical Development

The Pharmaceutical Development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the application. The studies described here are distinguished from routine control tests conducted according to specifications.

Additionally, this section should identify and describe the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance and drug product 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 application.

References:
- *ICH Guidelines: Q6A and Q6B*
- *ICH Q8 guidelines: Pharmaceutical Development*
- *ICH Q9 guidelines: Quality Risk Management*

3.2.2.2.1 Components of the Drug Product

3.2.2.2.1.1 Drug Substance

The compatibility of the drug substance with excipients listed in 3.2.2.1 should be discussed. Additionally, key physicochemical characteristics (e.g., water content, solubility, particle size distribution, polymorphic or solid state form) of the drug substance that can influence the performance of the drug product should be discussed.

For combination products, the compatibility of drug substances with each other should be discussed.

3.2.2.2.1.2 Excipients

The choice of excipients listed in 3.2.2.1, their concentration, their characteristics that can influence the drug product performance should be discussed relative to their respective functions.

3.2.2.2.2 Finished Pharmaceutical Product/Drug Product

3.2.2.2.2.1 Formulation Development

A brief summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage. The differences between clinical formulations and the formulation (i.e. composition) described in 3.2.2.1 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.

3.2.2.2.2.2 Overages

Any overages in the formulation(s) described in 3.2.2.1 should be justified.

3.2.2.2.2.3 Physicochemical and Biological Properties

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

3.2.2.2.3 Manufacturing Process Development

The selection and optimisation of the manufacturing process described in 3.2.2.3.3, in particular its critical aspects, should be explained. Where relevant, the method of sterilisation should be explained and justified.

Differences between the manufacturing process(es) used to produce pivotal clinical batches and the process described in 3.2.2.3.3 that can influence the performance of the product should be discussed.

Provide the formulation in tabular form for a typical batch and for an administration unit, e.g. one tablet, 5 ml of oral solution, or the contents of an ampoule or bag of large volume parenteral solution.

Include excipients that may be removed during processing, those that may not be added to every batch (e.g. acid and alkali), and the qualitative and quantitative composition of any tablet coating, capsule shell and inked imprint on the dosage form. State and justify any overages. State the function(s) of each excipient (e.g. antioxidant, lubricant and binder).

Where applicable special technical characteristics of excipients should be indicated, e.g. lyophilized, micronised, solubilized, emulsified. The type of water (e.g. purified, demineralized), where relevant, should be indicated.

Indicate any substances whose content may be varied (e.g. inked imprint, tablet coating). Ranges in the content of excipients need justification and explanation how the content is decided for each batch.

This section should identify, describe and document the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance and FPP quality, including stability.

(a) The compatibility of the API with excipients should be documented. 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 and supported by experimental data.
(b) The choice of excipients, in particular their functions and concentrations should be documented.
(c) For fixed-dose combination products, the compatibility of APIs with each other should be studied and the results documented.
(d) A discriminating dissolution method should be developed for the final composition of the FPP, when applicable. Limits should be set for each API in fixed-dose FPPs. The dissolution method should be incorporated into the stability and quality control programs. Multipoint dissolution profiles of both the test and the reference FPPs should be compared [multipoint: at least five (5)]. Dissolution testing should be incorporated into the stability programme.

    References:
    - *http://www.fda.gov/cder/guidance/1713bp1.pdf*
    - *WHO guideline on dissolution testing – Supplement 1, http://www.who.int/prequal/*

(e) A brief summary describing the development of the FPP should be provided, taking into consideration the proposed route of administration and usage.
(f) The selection and optimization of the manufacturing process, in particular its critical aspects, should be explained and documented. Where relevant, the method of sterilization should be explained and justified.
(g) Any overages in the formulation(s) should be warranted.
(h) 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.

    Usually, in this phase the microbial challenge test could be performed to establish and justify the amount of the antimicrobial preservatives to be used. For this purpose, the drug product should be formulated with different concentrations of preservatives and a microbial challenge test on each of the formulations will give the answer on the "least necessary" but still effective concentration.

(i) 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.

(j) A tabulated summary of the compositions of the FPP batches (batch number, batch size, manufacturing date and certificate of analysis at batch release) used in clinical trials and in bioequivalence studies and a presentation of dissolution profiles must be provided. A discussion of the documented information and data should be presented. Results from comparative in vitro studies (e.g., dissolution) or comparative in vivo studies (e.g., bioequivalence) should be discussed when appropriate.

Packaging should be selected to ensure the quality of the FPP throughout its shelf life.

Reference: *Validation of manufacturing processes*

http://whqlibdoc.who.int/trs/WHO_TRS_908.pdf#page=46

Prospective validation is carried out during the development stage by means of a risk analysis of the production process, which is broken down into individual steps; these are then evaluated on the basis of past experience to determine whether they might lead to critical situations. Where possible critical situations are identified, the risk is evaluated, the potential causes are investigated and assessed for probability and extent, the trial plans are drawn up, and the priorities set. The trials are then performed and evaluated, and an overall assessment is made. If, at the end, the results are acceptable, the process is satisfactory. Unsatisfactory processes must be modified and improved until a validation exercise proves them to be satisfactory.

3.2.2.2.4 Container Closure System

The suitability of the container closure system (described in 3.2.2.7) used for the storage, transportation (shipping) and use of the drug product 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 drug product).

3.2.2.2.5 Microbiological Attributes

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

3.2.2.2.6 Compatibility

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

3.2.2.2.7 Information from literature

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

3.2.2.3 Manufacture of the FPP

3.2.2.3.1 Sites of Manufacturer(s)

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.

State the name and street address of each facility where any aspect of manufacture of the FPP occurs, including production, sterilization, packaging and quality control. Indicate the activity performed at each site. Provide phone number(s); fax number(s) and e-mail addresses. Include any alternative manufacturing sites.

For each site where the major production step(s) is/are carried out, attach an original Certificate of a Pharmaceutical Product (CPP) issued by the competent authority in terms of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce.

Submit a valid GMP Certificate.

3.2.2.3.2 Batch Formula

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

3.2.2.3.3 Description of Manufacturing Process and Process Controls

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

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

Steps in the process should have the appropriate process parameters identified, such as time, temperature, or pH. Associated numeric values can be presented as an expected range. Numeric ranges for critical steps should be justified (e.g., blending parameters, loss on drying (LOD) of the compression blend and in-process as well as final yields). In certain cases, environmental conditions (e.g., experimentally documented temperature and relative humidity for hygroscopic FPPs) should be stated.

Proposals for the reprocessing of materials should be justified. Any data to support this justification should be either referenced or filed in this section (3.2.2.3.3)..

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

For sterile products, details of sterilization processes and/or aseptic procedures used must be described.

Stages of manufacture at which sampling is carried out for in-process control tests should be indicated. The in-process tests should be described in full, though reference to methods in other parts of the dossier or an acknowledged pharmacopoeia will suffice.

Documented evaluation of at least three (3) production scale batches should be submitted to provide assurance that the manufacturing process will reliably meet predetermined specifications.

Additionally for Biotech see 3.2.3.1 for facilities, if appropriate.

Reference ICH Guideline: Q6B

3.2.2.3.4 Manufacturing Process Controls of Critical Steps and Intermediates

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

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

Reference ICH Guidelines: Q2A, Q2B, Q6A, and Q6B

3.2.2.3.5 Process Validation and Evaluation

Description, documentation, and results of the validation and/or evaluation studies should be provided for critical steps or critical assays used in the manufacturing process (e.g., validation of the sterilisation process or aseptic processing or filling). Viral safety evaluation should be provided in 3.2.A.2, if necessary.

Reference ICH Guideline: Q6B

3.2.2.3.5.1 New FPPs

Data should be submitted in the application for demonstrating the validity of a given process.

Reference: *Validation of manufacturing processes http://whqlibdoc.who.int/trs/WHO_TRS_908.pdf#page=46*

Concurrent validation is carried out during normal production. This method is effective only if the development stage has resulted in a proper understanding of the fundamentals of the process. The first three production-scale batches must be monitored as comprehensively as possible. (This careful monitoring of the first three production batches is sometimes regarded as prospective validation.) The nature and specifications of subsequent in-process and final tests are based on the evaluation of the results of such monitoring.

One of the most practical forms of process validation, mainly for non-sterile products, is the final testing of the product to an extent greater than that required in routine quality control. It may involve extensive sampling, far beyond that called for in routine quality control and testing to normal quality control specifications, and often for certain parameters only. Thus, for instance, several hundred tablets per batch may be weighed to determine unit dose uniformity. The results are then treated statistically to verify the "normality" of the distribution, and to determine the standard deviation from the average weight. Confidence limits for individual results and for batch homogeneity are also estimated. Strong assurance is provided that samples taken at random will meet requirements if the confidence limits are well within compendial specifications.

Similarly, extensive sampling and testing may be performed with regard to any quality requirements. In addition, intermediate stages may be validated in the same way, e.g. dozens of samples may be assayed individually to validate mixing or granulation stages of low-dose tablet production by using the content uniformity test. Products (intermediate or final) may occasionally be tested for non-routine characteristics. Thus, sub-visual particulate matter in parenteral preparations may be determined by means of electronic devices, or tablets/capsules tested for dissolution profile if such tests are not performed on every batch.

Simulation process trials are used mainly to validate the aseptic filling of parenteral products that cannot be terminally sterilized. This involves filling ampoules with culture media under normal conditions, followed by incubation and control of microbial growth. In the past, a level of contamination of less than 0.3% was considered to be acceptable; however, the current target level should not exceed 0.1%.

Challenge experiments are performed to determine the robustness of the process, i.e. its capacity to operate smoothly when parameters approach acceptable limits. The use of ranges of parameters for the quality of the starting materials in experimental batches may make it possible to estimate the extent to which the process is still capable of producing an end-product that meets the specifications.

The progress from pre-formulation → formulation → pilot manufacture → industrial scale manufacture should be shown in the dossier submitted to be logical, reasoned and continuous.

Laboratory scale batches are produced at the research and early development laboratory stage; they may be of very small size (e.g. 100-1000x less than production scale). These batches may find many uses, for example to support formulation and packaging development, clinical and/or pre-clinical studies.

Pilot Batches may be used to support formal stability studies and also to support pre-clinical and clinical evaluation. Pilot batch size should correspond to at least 10% of the production scale batch, i.e. such that the multiplication factor for the scale-up does not exceed 10. For oral solid dosage forms this size should generally be 10% of production scale or 100,000 units whichever is the greater.

Full validation studies should be completed for each FPP at the production scale.

Where ranges of batch sizes are proposed, it should be shown that variations in batch size would not adversely alter the characteristics of the finished product. It is envisaged that those parameters listed in the following validation scheme will need to be re-validated once further scale-up is proposed after registration.

Where validation data on production scale batches are not provided with the application, the applicant shall submit the validation protocol described below. This should outline the formal process validation studies to be

conducted on production scale batches [usually not less than three (3) consecutive batches]. The applicant should submit a written commitment that information from these studies will be available for verification during inspection. The protocol should be in the dossier submitted and should include the following information as a minimum:

Short description of the process with a summary of the critical processing steps or critical parameters to be monitored during validation.

- FPP specification (release).
- Details of analytical methods (references to appropriate parts in the dossier). In-process controls proposed with acceptance criteria.
- Additional testing intended to be carried out (e.g. with proposed acceptance criteria and analytical validation as appropriate).
- Sampling plan — where, when and how the samples are taken.
- Drug content uniformity is considered essential for FDC-FPPs and should be addressed in the final process validation.
- Details of methods for recording and evaluation of results.
- Proposed timeframe

Following completion of the programme, a validation report containing the following information and signed by the appropriate authorized person should be generated for examination.

- Batch Analytical Data
- Certificates of Analysis
- Batch Production Records
- Report on unusual findings, modifications or changes found necessary with appropriate rationale
- Conclusions

Where the results obtained show significant deviations from those expected, PPB need to be informed immediately. In such cases corrective actions should be proposed and any changes proposed in the manufacturing process should receive prior PPB approval by way of variation.

3.2.2.3.5.2 Established Generics

Manufacturing as well as in-process and quality control testing data should be evaluated. Provide consecutive batches manufactured over the period of the last 12-24 months, should be used when reviewing the results, to provide a statistically significant picture. Trend analysis should be presented.

Rejected batches should not be included in the analysis but must be reported together with the reports of failure investigations.

3.2.2.4 Control of Excipients

3.2.2.4.1 Specifications for excipients

The specifications for excipients should be provided.

Include microbiological limits in the specification for excipients of natural origin. Skip testing is acceptable, if justified.

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

Provide detailed information on the avoidance and control of non-viral adventitious agents (e.g., transmissible spongiform encephalopathy agents (TSE-CEP is preferred), bacteria, mycoplasma, fungi). This information can include, for example, certification and/or testing of raw materials and excipients, and control of the production process, as appropriate for the material, process and agent.

For oils of plant origin (e.g., soy bean oil, peanut oil) demonstrate the absence of aflatoxins or biocides.

Only colours permitted by the EU's "List of permitted food colours", the FDA's "Inactive ingredient guide" or "Japanese Pharmaceutical Excipients" may be used.

References:

- *Reference ICH Guideline: Q6A and Q6B*
- *List of permitted food colours, Official journal of the European Communities, 1994. L237. (European Commission Directive 94/36/EC).*
- *Inactive ingredient guide. Rockville, MD, United States Food and Drug Administration, Division of Drug Information and Research, 1996.*
- *Japanese pharmaceutical excipients. Tokyo, Pharmaceutical and Cosmetics Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare (updated annually or biennially).*

3.2.2.4.1.1 Excipients not described in PhInt, JP, BP, PhEur or USP

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

Certificate of analysis for one batch of each excipient should be provided.

3.2.2.4.1.2 Excipients described in PhInt, JP, BP, PhEur or USP

Provide a copy of the monograph together with any test methods referenced in the monograph but not appearing in it. Note that the current monograph should always control the quality of the excipient. Provide details of any specifications additional to those in the pharmacopoeia.

Certificate of analysis for one batch of each excipient should be provided.

3.2.2.4.2 Analytical Procedures

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

Reference ICH Guidelines: Q2A and Q6B

3.2.2.4.3 Validation of Analytical Procedures

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

Reference ICH Guidelines: Q2A, Q2B, and Q6B

3.2.2.4.4 Justification of Specifications

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

Reference ICH Guidelines: Q3C and Q6B

3.2.2.4.5 Excipients of Human or Animal Origin

For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g., sources, specifications; description of the testing performed; viral safety data). (Details in 3.2.3.2).

Reference ICH Guidelines: Q5A, Q5D, and Q6B

3.2.2.5 Control of the Drug Product/ FPP

3.2.2.5.1 Specifications for the finished pharmaceutical product

The specification(s) for the drug product should be provided.

A list of general characteristics, specific standards, tests and limits for results for the FPP must be provided. Two separate sets of specifications may be set out: at manufacture (at release) and at the end of shelf life. Justification for the proposed specifications should be provided.
The control methods in the specification include:

- General characteristics of the pharmaceutical form (physicochemical properties and appearance);
- Identification tests of the API(s);
- Quantitative determination of API(s);
- Unless there is appropriate justification, the maximum acceptable deviation in the API content of the FPP shall not exceed ± 5% of the label claim at the time of manufacture;
- Purity tests [degradation products, residual solvents or other products (e.g. incompatibilities of APIs in a fixed-dose-combination (FDC) FPP] or process related impurities, microbial contamination);
- Pharmaceutical tests, e.g. dissolution;

- Physical tests appropriate to the dosage form, e.g. loss on drying, hardness, friability, particle size and apparent density;
- Uniformity of dosage units, where applicable;
- The identification tests for colouring materials used and identification and assay of antioxidants, antimicrobial or chemical preservatives with limits. The preservatives content limits of 90-110% at release are normally acceptable without further justification;
- For FDC-FPPs, analytical methods that can distinguish each API in the presence of the other APIs should be developed and validated;
- Acceptance criteria for degradants in FDC-FPPs should be established with reference to the API they are derived from. If an impurity results from a chemical reaction between two or more APIs, then its acceptance limits should be calculated with reference to the worst case (API with the smaller area under the curve). Alternatively, the content of such impurities could be calculated in relation to their reference standards;
- Dissolution testing specifications should include all APIs of the finished dosage form and utilize relevant media.

Information on the reference standards or reference materials used for testing of the FPP should be submitted if not previously provided in API part.

Reference:

- *ICH Q6A — Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances.*
- ICH Guidelines: Q3B and Q6B

3.2.2.5.2 Analytical procedures done to the FPP

All analytical test procedures, including biological and microbiological methods where relevant, must be described in sufficient detail to enable the procedures to be repeated if necessary.

If the product is tested on the basis of a monograph in a pharmacopoeia, it is sufficient to provide a copy of the monograph together with any test methods referenced in the monograph but not appearing in it. Provide details of any specifications and test methods additional to those in the pharmacopoeia.

3.2.2.5.3 Validation of analytical procedures

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

All non-compendial test procedures need to be validated. Results of the validation studies, comments on the choice of routine tests and standards must be provided. For pharmacopoeial methods, provide data to demonstrate that the method is applicable to this formulation.

Reference(s)

- *WHO Guideline: Validation of analytical procedures used in the examination of pharmaceutical materials*
- *WHO Expert Committee on Specifications for Pharmaceutical Preparations. 32nd report. Geneva, WHO, 1992 (WHO Technical Report Series, No. 823) in "Quality assurance of pharmaceuticals – A compendium of guidelines and related materials." Volume 1. WHO, Geneva, pp. 119-124 (1997)*
- *ICH-Q2A Text on Validation of Analytical Procedures*
- *ICH-Q2B Validation of Analytical Procedures: Methodology*
- ICH Guidelines: Q6B.

3.2.2.5.4 Batch analyses of the FPP

Results of not less than three (3) batch analyses (including the date of manufacture, place of manufacture, batch size and use of batch tested) must be presented. The batch analysis must include the results obtained for all specifications at release.

3.2.2.5.5 Characterisation of Impurities

Information on the characterisation of impurities should be provided, if not previously provided in "3.2.S.3.2 Impurities".

Reference ICH Guidelines: Q3B, Q5C, Q6A, and Q6B

3.2.2.5.6 Justification of Specification(s)

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

Reference ICH Guidelines: Q3B, Q6A, and Q6B

3.2.2.6 Reference Standards or Materials

Information on the reference standards or reference materials used for testing of the drug product should be provided, if not previously provided in "3.2.1.5 Reference Standards or Materials".

Reference ICH Guidelines: Q6A and Q6B

3.2.2.7 Container/closure system(s) and other packaging

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 3.2.2.2. The suitability of the container closure system 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).

Give a detailed description of the container/closure system(s), including any liner or wadding, and provide details of the composition of each component. Provide the specifications for any part of the container/closure system(s), which comes into contact with the product or is protective. For parenteral products, components that will at any stage come into contact with any part of the product must comply with requirements specified by the BP, Ph.Eur, JP or USP.

The specifications should include description and identification (and critical dimensions, with drawings where appropriate). Non-compendial methods (with validation) should be included where appropriate.

Describe other (e.g. outer) packaging, and state what materials they are made from.

3.2.2.7.1 Container labeling

All medicinal products shall be labelled in English and/or Kiswahili.

3.2.2.7.1.1 Labelling of the primary packaging

The applicant shall ensure that the primary (immediate) packaging of the product is labelled according to the law applicable in Kenya. The following minimum information shall be required in English on the label of the immediate packaging:

(a) brand name where appropriate
(b) International non-proprietary name/generic name
(c) Pharmaceutical dosage form, quantity of active ingredient per dosage unit
(d) total contents of container
(e) date of manufacture
(f) date of expiry
(g) batch number
(h) specific storage conditions
(i) name and full location address of manufacturer

Any drug product whose name, package or label bears close resemblance to an already registered product, or is likely to be mistaken for such a registered product, shall not be considered for registration. Disputes regarding trademark infringements not identified by PPB at the time of registration or amendment shall be the responsibility of the applicants. If however, valid safety concerns are identified, the new applicant shall be advised to make appropriate amendments.

Due to lack of space, the date of manufacture, address of the manufacturer and storage conditions may be omitted on the primary container if it is a blister or strip pack, or a vial or an ampoule less than 10mL.
The name of the manufacturer may be substituted with a trade-mark or other symbol.

Blisters and strips should include, as a minimum, the following information:

(a) Name, strength and pharmaceutical form of the FPP
(b) Name of the manufacturer
(c) The batch number assigned by the manufacturer
(d) The manufacturing and expiry dates in an uncoded form

However these details shall appear in full on the secondary packaging.

Labels shall not contain material written or graphical that targets to directly promote use of the products by infants and children. Pictograms intended to clarify certain information (e.g. age group for which product is intended, dosage e.t.c.) may be included on the product package.
All particulars on the label shall be easily legible, clearly comprehensible and indelible.

3.2.2.7.1.2 Labelling of outer packaging

Labelling of outer packaging or, where there is no outer packaging, on the immediate packaging labelling should include at least the following:

(a) The name of the FPP.
(b) Method of administration.
(c) A list of API(s) (using INNs if applicable) showing the amount of each present in a dosage unit, and a statement of the net contents of the container, e.g. number of dosage units, weight or volume.
(d) List of excipients known to be a safety concern for some patients, e.g. lactose, gluten, metabisulfites, parabens, ethanol, or tartrazine.
(e) Indication(s) and recommended dosage, where practicable
(f) The batch number assigned by the manufacturer.
(g) The manufacturing and expiry dates in an uncoded form.
(h) Storage conditions or handling precautions that may be necessary.
(i) Directions for use and any warnings or precautions that may be necessary.
(j) The name and address of the manufacturer
(k) The name and address of the company or person responsible for placing the product on the market if different from the manufacturer
(l) Kenya marketing authorization number (to be included after approval)
(m) Legal category

The labeled storage conditions should be achievable in practice in distribution network.
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 need only contain items (a), (b), (c), (g), (i) and (j) — or a logo that unambiguously identifies the company and the name of the dosage form or the route of administration.

3.2.2.8 Stability testing of the FPP

3.2.2.8.1 Stability Summary and Conclusion

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

The design of the formal stability studies for the finished product should be based on knowledge of the behaviour and properties of the API and the dosage form.

Describe the methodology used during stability studies; if this is identical to methodology described elsewhere in the data set, a cross-reference will suffice. If different methodology was used, the test procedures applied to the stability tests on the finished product should be validated or verified, and the accuracy as well as the precision (standard deviations) should be recorded. Characterize the possible degradants identified by stress stability testing (see 3.7.1 Stress testing (forced degradation) for details) during development pharmaceutics (compatibilities of the APIs with each other and with the excipients as well as the effect of temperature on the rate of degradation reactions). The tests for degradants should be validated to demonstrate that they are specific to the FPP being examined and are of adequate sensitivity.

Stability studies should be performed on each individual strength and container size of the finished product unless bracketing or matrixing is applied.

Other supporting data can be provided.

Reference ICH Guidelines: Q1A, Q1B, Q3B, and Q5C, Q6A

3.2.2.8.2 Post-approval Stability Protocol and Stability Commitment

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

When 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.
Where the submission includes long-term stability data on three production batches covering the proposed re-test period, a post approval commitment is considered unnecessary.

Otherwise, one of the following commitments should be made:

- If the submission includes data from stability studies on at least three production batches, a commitment should be made to continue these studies through the proposed re-test period.
- If the submission includes data from stability studies on fewer than three production batches, a commitment should be made to continue these studies through the proposed retest period and to place additional production batches, to a total of at least three, on long term stability studies through the proposed re-test period.
- If the submission does not include stability data on production batches, a commitment should be made to place the first three production batches on long term stability studies through the proposed re-test period.
- The stability protocol used for long-term studies for the stability commitment should be the same as that for the primary batches, unless otherwise scientifically justified.

Reference ICH Guidelines: Q1A and Q5C

3.2.2.8.3 Stability Data

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

Information on characterisation of impurities is located in 3.2.P.5.5.

Reference ICH Guidelines: Q1A, Q1B, Q2A, Q2B and Q5C

3.2.2.8.3.1 Stability-indicating quality parameters

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. 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.

Characteristics studied should be those in the finished product specification that are likely to be affected by storage and/or not monitored routinely at the time of manufacture, but which may be indicative of the stability/instability of the particular dosage form. These include:

- Physical characteristics (such as organoleptic properties, physical properties characteristic to the dosage form, important quality parameters, e.g., in vitro dissolution, moisture content and change of polymorphs, if relevant). As regards tablets and capsules packed with semi-permeable blister films, loss or uptake of water must be tested during stability studies.
- Efficacy of additives, such as antimicrobial agents, to determine whether such additives remain effective and within the accepted validated range throughout the projected shelf life.
- Chemical characteristics (assay of the API, content of degradation products, content of other ingredients such as preservatives, antioxidants, as well as enantiomeric purity, if relevant).
- Study of the container and closure interaction with the contents, when applicable.
- Where the product is to be diluted or reconstituted before being administered to the patient (e.g. a powder for injection or a concentrate for oral suspension) "in use" stability data must be submitted to support the recommended in-use storage time and conditions for those storage forms.

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 drug development on the product in its final formulation (except for preservative concentration intended for marketing. A single primary stability batch of the finished product should be tested for antimicrobial preservative effectiveness (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.

Report and discuss the results of stability testing as described in **Annex III.** Organize data for all attributes separately and evaluate each attribute in the report. No statistical analysis is required, if the stability data do not show variability or a trend over the time.

Shelf life acceptance criteria should be derived from consideration of all available stability information. The proposed storage conditions should be achievable in practice in Kenya.

The summary should include conclusions with respect to in-use storage conditions and shelf life, when applicable.

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

The post-approval stability protocol should also be provided and should be the same as that for the primary batches, unless otherwise scientifically justified.

Repackaging of bulk finished product will require stability studies in the bulk container and the final container closure system. Expiration dating is linked to the manufacturing date of the dosage form.

3.2.2.8.3.2 Photostability Testing

Photostability testing should be conducted on at least one primary batch of the FPP, if not included in the stress stability tests.

Reference:

- *ICH-Q1B: Photostability Testing of New Active Substances and Medicinal Products.*

3.2.2.8.3.3 Selection of Batches

At the time of submission data from stability studies should be provided for batches of the same formulation and dosage form in the container closure system proposed for marketing.

Stability data on three primary batches are to be provided. One of the three batches should be of production scale, the remaining two batches at least pilot scale. The composition, batch size, batch number and manufacturing date of each of the stability batches should be documented and the certificate of analysis at batch release should be attached.

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. Where possible, batches of the finished product should be manufactured by using different batches of the API.

3.2.2.8.3.4 Container Closure System

Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing (including, as appropriate, any secondary packaging and container label). Any available studies carried out on the product 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.

3.2.2.8.3.5 Testing Frequency

At the accelerated storage condition, a minimum of three points, including the initial and final time points (e.g., 0, 3, and 6 months), from a 6-month study is recommended. Where an expectation (based on development experience) exists that results from accelerated testing 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.

At long term storage condition, sampling should be done at initial, 3, 6, 9, 12, 18, 24, 36 etc. months to establish the stability characteristics of the FPP.

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.

Reference: *ICH Q1D: Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products*

3.2.2.8.3.6 Storage Conditions

In general, a FPP should be evaluated under storage conditions (with appropriate 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.

Stability testing of the finished product after constitution or dilution, if applicable, should be conducted to provide information for the labelling on the preparation, storage condition, and in-use period of the constituted or diluted product. This testing should be performed on the constituted or diluted product through the proposed in-use period on primary batches as part of the formal stability studies at initial and final time points and, if full shelf life long term data will not be available before submission, at six months or the last time point for which data will be available. In general, this testing need not be repeated on commitment batches.

Note: in-use stability testing should be performed on at least two different batches one of which should be investigated close to the end of shelf life.

The long term testing should cover a minimum **of 12 months duration** at the time of submission and should be continued for a period of time sufficient to cover the proposed shelf life. Additional data accumulated during the assessment period of the registration application should be submitted to PPB 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 finished products are detailed in **Annex III**. The general case applies if a subsequent section does not specifically cover the finished product.

3.2.2.8.3.6.1 General case

Storage temperature (°C)	Relative humidity (%)	Minimum time period covered by data at submission
Accelerated: 40±2	75±5	6
Long term: 30±2	65±5	12

Note. 30°C ± 2°C/65% RH ± 5% RH is the long term stability condition for products to be marketed in Kenya, unless otherwise justified for other harsh conditions.

When a "significant change" occurs at any time during 6 months' testing at the accelerated storage condition, these should be evaluated during long term stability testing.

In general, "significant change" for a finished product is defined as:

- A 5% change in assay from its initial value; or failure to meet the acceptance criteria for potency when using biological or immunological procedures.
- Any degradation product exceeding its acceptance criterion.
- Failure to meet the acceptance criteria for appearance, physical attributes, and functionality test (e.g., colour, phase separation, hardness).
- And, as appropriate for the dosage form:
  - ❖ Failure to meet the acceptance criterion for pH; or
  - ❖ Failure to meet the acceptance criteria for dissolution for 12 dosage units.

3.2.2.8.3.6.2 Drug substances intended for storage in a refrigerator

Study Storage condition Minimum time period covered by data at submission

Storage temperature (°C)	Relative humidity (%)	Minimum time period covered by data at submission
Accelerated: 25±2	60±5	6
Long term: 5±3	-	12

Data from refrigerated storage should be assessed according to the evaluation section of this guideline, except where explicitly noted below.
If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed re-test period should be based on the real time data available at the long term storage condition.
If significant change occurs within the first 3 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 drug substance for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a drug substance through 6 months when a significant change has occurred within the first 3 months.

3.2.2.8.3.6.3 Drug substances intended for storage in a freezer

Study Storage condition Minimum time period covered by data at submission

Storage temperature (°C)	Minimum time period covered by data at submission
Long term: 20±5	12

For drug substances intended for storage in a freezer, the re-test period should be based on the real time data obtained at the long term storage condition. In the absence of an accelerated storage condition for drug substances 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) 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.

3.2.2.8.3.6.4 Drug substances intended for storage below -20°C

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

Reference: *ICH Topic Q 1 A (R2) Stability Testing of new Drug Substances and Products*

3.2.2.8.3.6.5 Finished products packaged in impermeable containers

Sensitivity to moisture or potential for solvent loss is not a concern for finished products 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 humidity condition.

3.2.2.8.3.6.6 Finished products 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 defined below.

Study	Storage condition	Minimum time period covered by data at submission (months)
Long term	30±2 °C/65±5% RH	12
Accelerated	40±2 °C/NMT 25±5% RH	6

Note. Unless otherwise justified, 30 ± 2 °C and 65 ± 5% RH is the long term stability condition for products to be marketed in Kenya.

Ultimately, it should be demonstrated that aqueous-based finished products stored in semi-permeable containers could withstand low relative humidity environments. Other comparable approaches can be developed and reported for non-aqueous, solvent-based products.

A 5% loss in water from its initial value is considered a significant change for a FPP packaged in a semi-permeable container after three (3) months storage at 40 ± 2 °C and NMT 25 ± 5% RH.

3.2.2.8.4 Evaluation

A systematic approach should be adopted in 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, hardness, LOD, etc.).

The purpose of the stability study is to establish, based on testing a minimum of three batches of the finished product, a shelf life and label storage instructions applicable to all future batches of the finished product manufactured and packaged 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 formal statistical analysis; providing a justification for the omission should be sufficient.

An approach for analyzing 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. 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.

Reference*: ICH-Q1E Evaluation For Stability Data*

3.2.2.8.5 Extrapolation of data

An API is considered as stable if it is within the defined specifications when stored at 30 ± 2 °C/65 ± 5 % RH (2 years) and 40 ± 2 °C/75 ± 5 % RH (6 months).

If long term data are supported by results from accelerated studies the re-test period/shelf life may be extended beyond the end of long-term studies. The proposed retest period or shelf life can be up to twice, but should not be more than 12 months beyond, the period covered by long-term data.

Reference: *ICH-Q1E Evaluation For Stability Data*

3.2.2.8.6 Core Storage Statements

Testing conditions where stability has been shown	**Required labelling statement**	**Additional labelling statement*, where relevant**
30 °C/65% RH (long term) 40 °C/75% RH (accelerated)	None**	Do not refrigerate or freeze
30 °C/65% RH (long term)	Do not store above 30 °C, or Store below 30 °C	Do not refrigerate or freeze
25 °C/60% RH (long term)	Do not store above 25 °C, or Store below 25 °C	Do not refrigerate or freeze

* Depending on the pharmaceutical form and the properties of the product, there may be a risk of deterioration due to physical changes if subjected to low temperatures. Low temperatures may also have an effect on the packaging in certain cases. An additional statement may be necessary to take account of this possibility.

**The following SPC and PIL statements are required: this FPP does not require any special storage conditions

3.2.3 APPENDICES

3.2.3.1 Facilities and Equipment

Biotech:

A diagram should be provided illustrating the manufacturing flow including movement of raw materials, personnel, waste, and intermediate(s) in and out of the manufacturing areas. Information should be presented with respect to adjacent areas or rooms that may be of concern for maintaining integrity of the product.

Information on all developmental or approved products manufactured or manipulated in the same areas as the applicant's product should be included.

A summary description of product-contact equipment, and its use (dedicated or multi-use) should be provided. Information on preparation, cleaning, sterilisation, and storage of specified equipment and materials should be included, as appropriate.

Information should be included on procedures (e.g., cleaning and production scheduling) and design features of the facility (e.g., area classifications) to prevent contamination or cross-contamination of areas and equipment, where operations for the preparation of cell banks and product manufacturing are performed.

3.2.3.2 Adventitious Agents Safety Evaluation

Information assessing the risk with respect to potential contamination with adventitious agents should be provided in this section.

3.2.3.2.1 For non-viral adventitious agents:

Detailed information should be provided on the avoidance and control of non-viral adventitious agents (e.g., transmissible spongiform encephalopathy agents, bacteria, mycoplasma, fungi). This information can include, for example, certification and/or testing of raw materials and excipients, and control of the production process, as appropriate for the material, process and agent.

Reference ICH Guidelines: Q5A, Q5D, and Q6B

3.2.3.2.2 For viral adventitious agents:

Detailed information from viral safety evaluation studies should be provided in this section. Viral evaluation studies should demonstrate that the materials used in production are considered safe, and that the approaches used to test, evaluate, and eliminate the potential risks during manufacturing are suitable. The applicant should refer to Q5A, Q5D, and Q6B for further guidance.

Materials of Biological Origin

Information essential to evaluate the virological safety of materials of animal or human origin (e.g. biological fluids, tissue, organ, cell lines) should be provided. (See related information in 3.2.1.2.3, and 3.2.2.4.5). For cell lines, information on the selection, testing, and safety assessment for potential viral contamination of the cells and viral qualification of cell banks should also be provided. (See related information in 3.2.1.2.3).

Testing at appropriate stages of production

The selection of virological tests that are conducted during manufacturing (e.g., cell substrate, unprocessed bulk or post viral clearance testing) should be justified. The type of test, sensitivity and specificity of the test, if applicable, and frequency of testing should be included. Test results to confirm, at an appropriate stage of manufacture, that the product is free from viral contamination should be provided. (See related information in 3.2.1.2.4 and 3.2.2.3.4).

Viral Testing of Unprocessed Bulk

In accordance with Q5A and Q6B, results for viral testing of unprocessed bulk should be included.

Viral Clearance Studies

In accordance with Q5A, the rationale and action plan for assessing viral clearance and the results and evaluation of the viral clearance studies should be provided. Data can include those that demonstrate the validity of the scaled-down model compared to the commercial scale process; the adequacy of viral inactivation or removal procedures for manufacturing equipment and materials; and manufacturing steps that are capable of removing or inactivating viruses. (See related information in 3.2.S.2.5 and 3.2.2.3.5).

Reference ICH Guidelines: Q5A, Q5D, and Q6B

3.2.3.3 Novel Excipients

For novel excipients: a dossier should be established containing the same data as required for new active substances:

a) A strict definition of the excipient, its function and its conditions of use. If the excipient is complex or is made of a mixture of compounds, the composition should be specified in qualitative and quantitative terms.
b) For novel excipients and for excipients presented as a mixture of compounds the following should be taken into consideration:
    i. Any bibliographical data on the chemistry and on the toxicology and the field in which the product is already used.
    ii. The provisions concerning additives in foodstuffs: any criteria which are based on the toxicological data, with cross-references to these data. The quality specifications which have been laid down in the directives are satisfactory as long as the routine control tests used are validated.
    iii. The international specifications (FAO/WHO/JECFA), and other publications such as the Food Chemical Codex.
    iv. For medicinal products for cutaneous use, data on the starting material in cosmetic products.
    v. Data concerning the toxicology of the novel excipient should be presented according to the dosage form and the route of administration of the medicinal product (if applicable).
c) Documentation on chemistry of excipients is required for all new excipients, just as Chemistry of New Active Substances.

MODULE 4: NONCLINICAL STUDY REPORTS FOR NEW CHEMICAL ENTITIES ONLY

This guideline presents the organisation of the nonclinical reports in the applications that will be submitted. 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 appropriate location for individual-animal data is in the study report or as an appendix to the study report.

4.1 Table of Contents of Module 4

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

4.2 Study Reports

The study reports should be presented in the following order:

4.2.1 Pharmacology

4.2.1.1 Primary Pharmacodynamics

4.2.1.2 Secondary Pharmacodynamics

4.2.1.3 Safety Pharmacology

4.2.1.4 Pharmacodynamic Drug Interactions

4.2.2 Pharmacokinetics

4.2.2.1 Analytical Methods and Validation Reports (if separate reports are available)

4.2.2.2 Absorption

4.2.2.3 Distribution

4.2.2.4 Metabolism

4.2.2.5 Excretion

4.2.2.6 Pharmacokinetic Drug Interactions (nonclinical)

4.2.2.7 Other Pharmacokinetic Studies

4.2.3 Toxicology

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

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

4.2.3.3 Genotoxicity

4.2.3.3.1 In vitro

4.2.3.3.2 In vivo (including supportive toxicokinetics evaluations)

4.2.3.4 Carcinogenicity (including supportive toxicokinetics evaluations)

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

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

4.2.3.4.3 Other studies

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

4.2.3.5.1 Fertility and early embryonic development

4.2.3.5.2 Embryo-fetal development

4.2.3.5.3 Prenatal and postnatal development, including maternal function

4.2.3.5.4 Studies in which the offspring (juvenile animals) are dosed and/or further evaluated.

4.2.3.6 Local Tolerance

4.2.3.7 Other Toxicity Studies (if available)

4.2.3.7.1 Antigenicity

4.2.3.7.2 Immunotoxicity

4.2.3.7.3 Mechanistic studies (if not included elsewhere)

4.2.3.7.4 Dependence

4.2.3.7.5 Metabolites

4.2.3.7.6 Impurities

4.2.3.7.7 Other

References:

- *Non-Clinical Safety Studies For The Conduct Of Human Clinical Trials For Pharmaceuticals (ICH M3[R2]) modification;* ***http://www.ema.europa.eu/pdfs/human/ich/028695en.pdf***
- *EMEA: Non- Clinical Scientific Guidelines; http://www.ema.europa.eu/htms/human/humanguidelines/nonclinical.htm*
- ***CTD M4S (R2) SAFETY****; http://www.ich.org/LOB/media/MEDIA556.pdf*

4.3 Literature References

MODULE 5: CLINICAL STUDY REPORTS

This part provides guidance on the organization of the study reports, other clinical data, and references within an application for registration of a pharmaceutical product. These elements should facilitate the preparation and review of a marketing application.

This guideline is not intended to indicate what studies are required for successful registration. It indicates an appropriate organization for the clinical study reports that are in the application.

This guideline recommends a specific organization for the placement of clinical study reports and related information to simplify preparation and review of dossiers and to ensure completeness. The placement of a report should be determined by the primary objective of the study. Each study report should appear in only one section. Where there are multiple objectives, the study should be cross-referenced in the various sections. An explanation such as "not applicable" or "no study conducted" should be provided when no report or information is available for a section or subsection.

5.1 NEW CHEMICAL ENTITIES ONLY

5.1.1 Table of Contents of Module 5: A Table of Contents for study reports should be provided

5.1.2 Tabular Listing of All Clinical Studies

A tabular listing of all clinical studies and related information should be provided. For each study, this tabular listing should generally include the type of information identified in Table 5.1.1. of this guideline. Other information can be included in this table if the applicant considers it useful. The sequence in which the studies are listed should follow the sequence described in Section 5.1.3 below. Use of a different sequence should be noted and explained in an introduction to the tabular listing

5.1.3 Clinical Study Reports

5.1.3.1 Reports of Biopharmaceutic Studies

BA studies evaluate the rate and extent of release of the active substance from the medicinal product. Comparative BA or BE studies may use PK, PD, clinical, or *in vitro* dissolution endpoints, and may be either single dose or multiple dose. When the primary purpose of a study is to assess the PK of a drug, but also includes BA information, the study report should be submitted in Section 5.1.3.1, and referenced in Sections 5.1.3.1.1 and/or 5.1.3.1.2.

5.1.3.1.1 Bioavailability (BA) Study Reports

BA studies in this section should include

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

5.1.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports

Studies in this section compare the rate and extent of release of the drug substance from similar drug products (e.g., tablet to tablet, tablet to capsule). Comparative BA or BE studies may include comparisons between

4.2.1 the drug product used in clinical studies supporting effectiveness and the to-be-marketed drug product,

4.2.2 the drug product used in clinical studies supporting effectiveness and the drug product used in stability batches, and

4.2.3 similar drug products from different manufacturers.

5.1.3.1.3 In Vitro – In Vivo Correlation Study Reports

In vitro dissolution studies that provide BA information, including studies used in seeking to correlate *in vitro* data with *in vivo* correlations, should be placed in Section 5.1.3.1.3. Reports of *in vitro* dissolution tests used for batch quality control and/or batch release should be placed in the module 3.

5.1.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

Bioanalytical and/or analytical methods for biopharmaceutic studies or *in vitro* dissolution studies should ordinarily be provided in individual study reports. Where a method is used in multiple studies, the method and

its validation should be included once in Section 5.1.3.1.4 and referenced in the appropriate individual study reports.

5.1.3.2 Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials

Human biomaterials is a term used to refer to proteins, cells, tissues and related materials derived from human sources that are used *in vitro* or ex vivo to assess PK properties of drug substances. Examples include cultured human colonic cells that are used to assess permeability through biological membranes and transport processes, and human albumin that is used to assess plasma protein binding. Of particular importance is the use of human biomaterials such as hepatocytes and/or hepatic microsomes to study metabolic pathways and to assess drug-drug interactions with these pathways. Studies using biomaterials to address other properties (e.g., sterility or pharmacodynamics) should not be placed in the Clinical Study Reports Section, but in the Nonclinical Study Section (Module 4).

5.1.3.2.1 Plasma Protein Binding Study Reports

Ex vivo protein binding study reports should be provided here. Protein binding data from PK blood and/or plasma studies should be provided in Section 5.1.3.3.

5.1.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies

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

5.1.3.2.3 Reports of Studies Using Other Human Biomaterials

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

5.1.3.3 Reports of Human Pharmacokinetic (PK) Studies

Assessment of the PK of a drug in healthy subjects and/or patients is considered critical to designing dosing strategies and titration steps, to anticipating the effects of concomitant drug use, and to interpreting observed pharmacodynamic differences. These assessments should provide a description of the body's handling of a drug over time, focusing on maximum plasma concentrations (peak exposure), area-under-curve (total exposure), clearance, and accumulation of the parent drug and its metabolite(s), in particular those that have pharmacological activity.

The PK studies whose reports should be included in Sections 5.1.3.3.1 and 5.1.3.3.2 are generally designed to (1) measure plasma drug and metabolite concentrations over time, (2) measure drug and metabolite concentrations in urine or faeces when useful or necessary, and/or (3) measure drug and metabolite binding to protein or red blood cells.

On occasion, PK studies may include measurement of drug distribution into other body tissues, body organs, or fluids (e.g., synovial fluid or cerebrospinal fluid), and the results of these tissue distribution studies should be included in Section 5.1.3.3.1 to 5.1.3.3.2, as appropriate. These studies should characterise the drug's PK and provide information about the absorption, distribution, metabolism, and excretion of a drug and any active metabolites in healthy subjects and/or patients. Studies of mass balance and changes in PK related to dose (e.g., determination of dose proportionality) or time (e.g., due to enzyme induction or formation of antibodies) are of particular interest and should be included in Sections 5.1.3.3.1 and/or 5.1.3.3.2. Apart from describing mean PK in normal and patient volunteers, PK studies should also describe the range of individual variability. In the ICH E5 guideline on Ethnic Factors in the Acceptance of Foreign Data, factors that may result in different responses to a drug in different populations are categorised as intrinsic ethnic factors or extrinsic ethnic factors. In this document, these categories are referred to as intrinsic factors and extrinsic factors, respectively. Additional studies can also assess differences in systemic exposure as a result of changes in PK due to intrinsic (e.g., age, gender, racial, weight, height, disease, genetic polymorphism, and organ dysfunction) and extrinsic (e.g., drug-drug interactions, diet, smoking, and alcohol use) factors. Reports of PK studies examining the influence of intrinsic and extrinsic factors on exposure should be organised in Sections 5.1.3.3.3 and 5.1.3.3.4, respectively.

In addition to standard multiple-sample PK studies, population PK analyses based on sparse sampling during clinical studies can also address questions about the contributions of intrinsic and extrinsic factors to the variability in the dose-PK-response relationship. Because the methods used in population PK studies are substantially different from those used in standard PK studies, these studies should be placed in Section 5.1.3.3.5.

5.1.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports

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

5.1.3.3.2 Patient PK and Initial Tolerability Study Reports

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

5.1.3.3.3 Intrinsic Factor PK Study Reports

Reports of PK studies to assess effects of intrinsic factors, should be placed in this section.

5.1.3.3.4 Extrinsic Factor PK Study Reports

Reports of PK studies to assess effects of extrinsic factors, should be placed in this section.

5.1.3.3.5 Population PK Study Reports

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

5.1.3.4 Reports of Human Pharmacodynamic (PD) Studies

Reports of studies with a primary objective of determining the PD effects of a drug product in humans should be placed in this section. Reports of studies whose primary objective is to establish efficacy or to accumulate safety data, however, should be placed in Section 5.1.3.5.

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

Dose-finding, PD and/or PK-PD studies can be conducted in healthy subjects and/or patients, and can also be incorporated into the studies that evaluate safety and efficacy in a clinical indication. Reports of dose-finding, PD and/or PK/PD studies conducted in healthy subjects should be placed in Section 5.1.3.4.1, and the reports for those studies conducted in patients should be placed in Section 5.1.3.4.2.

In some cases, the short-term PD, dose-finding, and/or PK-PD information found in pharmacodynamic studies conducted in patients will provide data that contribute to assessment of efficacy, either because they show an effect on an acceptable surrogate marker (e.g., blood pressure) or on a clinical benefit endpoint (e.g., pain relief). Similarly, a PD study may contain important clinical safety information. When these studies are part of the efficacy or safety demonstration, they are considered clinical efficacy and safety studies that should be included in Section 5.1.3.5, not in Section 5.1.3.4.

5.1.3.4.1 Healthy Subject PD and PK/PD Study Reports

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

5.1.3.4.2 Patient PD and PK/PD Study Reports

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

5.1.3.5 Reports of Efficacy and Safety Studies

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

Within Section 5.1.3.5, studies should be organised by design (controlled, uncontrolled) and, within controlled studies, by type of control. Within each section, studies should be categorized further, ordered by whether the study report is complete or abbreviated (ICH E3), with completely reported studies presented first. Published reports with limited or no further data available to the sponsor should be placed last in this section.

In cases where the application includes multiple therapeutic indications, the reports should be organized in a separate Section 5.1.3.5 for each indication. In such cases, if a clinical efficacy study is relevant to only one of the indications included in the application, it should be included in the appropriate Section 5.1.3.5; if a clinical

efficacy study is relevant to multiple indications, the study report should be included in the most appropriate Section 5.1.3.5 and referenced as necessary in other Sections 5.1.3.5, e.g., Section 5.1.3.5A, Section 5.1.3.5B.

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

The controlled clinical study reports should be sequenced by type of control:

Placebo control (could include other control groups, such as an active comparator or other doses)

No-treatment control

Dose-response (without placebo)

Active control (without placebo)

External (Historical) control, regardless of the control treatment

Within each control type, where relevant to assessment of drug effect, studies should be organized by treatment duration. Studies of indications other than the one proposed in the application, but that provide support for efficacy in the proposed use, should be included in Section 5.1.3.5.1.

Where a pharmacodynamic study contributes to evidence of efficacy, it should be included in Section 5.1.3.5.1. The sequence in which studies were conducted is not considered pertinent to their presentation. Thus, placebo-controlled trials, whether early or late, should be placed in Section 5.1.3.5.1. Controlled safety studies, including studies in conditions that are not the subject of the application, should also be reported in Section 5.1.3.5.1.

5.1.3.5.2 Study Reports of Uncontrolled Clinical Studies

Study reports of uncontrolled clinical studies (e.g., reports of open label safety studies) should be included in Section 5.1.3.5.2. This includes studies in conditions that are not the subject of the marketing application.

5.1.3.5.3 Reports of Analyses of Data from More than One Study

Many clinical issues in an application can be addressed by an analysis considering data from more than one study. The results of such an analysis should generally be summarized in the clinical summary documents, but a detailed description and presentation of the results of such analyses are considered critical to their interpretation. Where the details of the analysis are too extensive to be reported in a summary document, they should be presented in a separate report. Such reports should be placed in Section 5.1.3.5.3. Examples of reports that would be found in this section include: a report of a formal meta-analysis or extensive exploratory analysis of efficacy to determine an overall estimate of effect size in all patients and/or in specific subpopulations, and a report of an integrated analysis of safety that assesses such factors as the adequacy of the safety database, estimates of event rates, and safety with respect to variables such as dose, demographics, and concomitant medications. A report of a detailed analysis of bridging, considering formal bridging studies, other relevant clinical studies, and other appropriate information (e.g., PK and PD information), should be placed in this section if the analysis is too lengthy for inclusion in the Clinical Summary.

5.1.3.5.4 Other Study Reports

This section can include:

- Reports of interim analyses of studies pertinent to the claimed indications
- Reports of controlled safety studies not reported elsewhere
- Reports of controlled or uncontrolled studies not related to the claimed indication
- Published reports of clinical experiences with the medicinal product that are not included in Section 5.1.3.5.1. However, when literature is important to the demonstration or substantiation of efficacy, it should be included in Section 5.1.3.5.1
- Reports of ongoing studies

5.1.3.6 Reports of Post-Marketing Experience

For products that are currently marketed, reports that summarize marketing experience (including all significant safety observations) should be included in Section 5.1.3.6.

5.1.3.7 Case Report Forms and Individual Patient Listings

Case report forms and individual patient data listings that are described as appendices 16.3 and 16.4 in the ICH clinical study report guideline, should be placed in this section when submitted, in the same order as the clinical study reports and indexed by study.

5.1.4 Literature References

Copies of referenced documents, including important published articles, official meeting minutes, or other regulatory guidance or advice should be provided here. This includes copies of all references cited in the Clinical Overview, and copies of important references cited in the Clinical Summary or in the individual technical reports that were provided in Module 5, section 5.1.3. Only one copy of each reference should be provided. Copies of references that are not included here should be immediately available on request.

5.2 INTERCHANGEABILITY OF GENERIC DRUGS – (GENERIC DRUG APPLICATIONS ONLY)

5.2.1 Reports of Biopharmaceutic Studies

BA studies evaluate the rate and extent of release of the active substance from the medicinal product. Comparative BA or BE studies may use PK, PD, clinical, or *in vitro* dissolution endpoints, and may be either single dose or multiple dose. When the primary purpose of a study is to assess the PK of a drug, but also includes BA information, the study report should be submitted in Section 5.1.3.1, and referenced in Sections 5.1.3.1.1 and/or 5.1.3.1.2.

5.2.1.1 Bioavailability (BA) Study Reports

BA studies in this section should include

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

5.2.1.1.1 Comparative BA and Bioequivalence (BE) Study Reports

Studies in this section compare the rate and extent of release of the drug substance from similar drug products (e.g., tablet to tablet, tablet to capsule). Comparative BA or BE studies may include comparisons between

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

5.2.1.1.1.1 General Notes on Bioequivalence Study Report

Multi-source drug products need to conform to the same standards of quality, efficacy and safety required of the originator's product. In addition, reasonable assurance must be provided that they are, as intended, clinically interchangeable with nominally equivalent market products.

With some classes of products, including-most evidently parenteral formulations of highly water-soluble compounds, interchangeability is adequately assured by implementation of Good Manufacturing Practices and evidence of conformity with relevant pharmacopoeial specifications. For other classes of products, including biologicals such as vaccines, animal sera, and products derived from human blood and plasma, and products manufactured by biotechnology, the concept of interchangeability raises complex considerations that are not addressed in this document, and these products are consequently excluded from consideration. However, for most nominally equivalent pharmaceutical products (including most solid oral dosage forms), a demonstration of therapeutic equivalence can and should be carried out, and such assessment should be included in the documentation for marketing authorization. Orally or parenterally administered aqueous solutions will be assessed by chemical-pharmaceutical characteristics only.

This guideline refers to the marketing of pharmaceutical products that are intended to be therapeutically equivalent, and thus interchangeable, but produced by different manufacturers.
Bioequivalence studies are designed to compare the in vivo performance of a test pharmaceutical product (multi-source) compared to a reference pharmaceutical product and the report should be as per WHO** guidelines.

Reference:

***WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report. Geneva, World Health Organization, 2006: 347-458 (WHO Technical Report Series, No.937).*
***WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report. Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902):161–180.*

Bio-equivalence study report should contain at least the following items as described in part 2 of the application form see Annex I:

- Description of study design. The most appropriate study type is two-period, randomized, crossover study. If other study types were used (e.g. parallel group design), these should be justified by the applicant. In general, single-dose study with sufficiently long period for blood samples collection is acceptable.
- Information about investigators, study site and study dates.
- Data about preparations used: manufacturer, place of manufacture, batch number etc. Reference preparation in bio-equivalence study should be innovator preparation or product registered by PPB, ICH and associated countries or from WHO list of international comparator products if listed.

Reference: *Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products. 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.*

- Characterization of study subjects. Bio-equivalence study should be normally performed in healthy volunteers. If patients were used, this should be justified by the applicant. Number of subjects should not be less than 12. Study report should contain inclusion and exclusion criteria, listing of demographic data of all subjects.
- Description of study procedures. Administration of test products, meals, times of blood sampling or urine collection periods should be described in the clinical report.
- Description and validation of drug determination methods in investigated material. Analytical method should be validated over the measured drug concentration range. Validation should contain methodology and results of sensitivity, specificity, accuracy, precision and repeatability determination.
- All measured drug concentrations should be presented.
- Calculation methodology of pharmacokinetic parameters. Preferred is non-compartmental analysis. If modelled parameters were used, these models should be validated for the compound. All measured and calculated pharmacokinetic parameters should be presented in the report.
- Description of statistical methodology and results of statistical calculations. Statistical calculations should be based on the equivalence evaluation. The statistical method of choice is the two one-sided test procedure and the calculation of 90% confidence intervals of the test/reference ratios of pharmacokinetic parameters. The main parameters to assess the bio-equivalence are area under the plasma concentration-time curve (AUC) and maximum concentrations (C_{max}) ratios.

  The 90% confidence interval for the AUC-ratio should lie within a bio-equivalence range of 80-125%. In some specific cases of drugs with a narrow therapeutic range the acceptance range may need to be tightened.

  The 90% confidence interval for the C_{max}-ratio should lie within a bio-equivalence range of 80-125%. In some specific cases of drugs with a narrow therapeutic range the acceptance range may need to be tightened. In certain cases for drugs with an inherently high intra-subject variability, a wider acceptance range (e.g., 75-133%) may be acceptable. The range used must be defined prospectively and should be justified, taking into account safety and efficacy considerations.

Reference: EMEA, as described in "Guideline On The Investigation Of Bioequivalence 2010", available at: http://www.ema.europa.eu/pdfs/human/qwp/140198enrev1fin.pdf

5.2.1.1.2 In Vitro – In Vivo Correlation Study Reports

In vitro dissolution studies that provide BA information, including studies used in seeking to correlate *in vitro* data with *in vivo* correlations, should be placed in Section 5.1.3.1.3. Reports of *in vitro* dissolution tests used for batch quality control and/or batch release should be placed in the module 3.

5.2.1.1.3 Reports of Bioanalytical and Analytical Methods for Human Studies

Bioanalytical and/or analytical methods for biopharmaceutic studies or *in vitro* dissolution studies should ordinarily be provided in individual study reports. Where a method is used in multiple studies, the method and

its validation should be included once in Section 5.1.3.1.4 and referenced in the appropriate individual study reports.

5.2.1.2 *In vitro* dissolution tests

General aspects of *in vitro* dissolution experiments are briefly outlined in **Dissolution testing and Similarity of Dissolution Profiles (below)** including basic requirements how to use the similarity factor (*f2*-test).

5.2.1.2.1 *In vitro* dissolution tests complementary to bioequivalence studies

The results of *in vitro* dissolution tests at three different buffers (normally pH 1.2, 4.5 and 6.8) and the media intended for drug product release (QC media), obtained with the batches of test and reference 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 reference product **(see Dissolution testing and Similarity of Dissolution Profiles below**).

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.

5.2.1.2.2 *In vitro* dissolution tests in support of biowaiver of strengths

Appropriate *in vitro* dissolution should confirm the adequacy of waiving additional *in vivo* bioequivalence testing. Accordingly, dissolution should be investigated at different pH values as outlined in the previous section (normally pH 1.2, 4.5 and 6.8) unless otherwise justified. Similarity of *in vitro* dissolution **(see Dissolution testing and Similarity of Dissolution Profiles below**) 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 reference medicinal 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).

5.2.1.2.2.1 Dissolution testing and Similarity of Dissolution Profiles

1. General aspects of dissolution testing as related to bioavailability

During the development of a medicinal product a dissolution test is used as a tool to identify formulation factors that are influencing and may have a crucial effect on the bioavailability of the drug. As soon as the composition and the manufacturing process are defined a dissolution test is used in the quality control of scale-up and of production batches to ensure both batch-to-batch consistency and that the dissolution profiles remain similar to those of pivotal clinical trial batches. Furthermore, in certain instances a dissolution test can be used to waive a bioequivalence study.

Therefore, dissolution studies can serve several purposes:

(i) Testing on product quality
- To get information on the test batches used in bioavailability/bioequivalence studies and pivotal clinical studies to support specifications for quality control
- To be used as a tool in quality control to demonstrate consistency in manufacture
- To get information on the reference product used in bioavailability/bioequivalence studies andpivotal clinical studies.

(ii) Bioequivalence surrogate inference
- To demonstrate in certain cases similarity between different formulations of an active substance and the reference medicinal product

- 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.

2. 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 $f2$ statistic as follows:
In this equation $f2$ is the similarity factor, n is the number of time points, R(t) is the mean percent reference drug dissolved at time t after initiation of the study; T(t) is the mean percent test drug dissolved at time t after initiation of the study. For both the reference and test formulations, percent dissolution should be determined.

The evaluation of the similarity factor is based on the following conditions:
- A minimum of three time points (zero excluded)
- The time points should be the same for the two formulations
- Twelve individual values for every time point for each formulation
- Not more than one mean value of > 85% dissolved for any of the formulations.
- The relative standard deviation or coefficient of variation of any product should be less than 20% for the first point and less than 10% from second to last time point.

An *f2* value between 50 and 100 suggests that the two dissolution profiles are similar.

When the $f2$ statistic is not suitable, then the similarity may be compared using model-dependent or model-independent methods e.g. by statistical multivariate comparison of the parameters of the Weibull function or the percentage dissolved at different time points.

Alternative methods to the $f2$ statistic to demonstrate dissolution similarity are considered acceptable, if statistically valid and satisfactorily justified.

The similarity acceptance limits should be pre-defined and justified and not be greater than a 10% difference. In addition, the dissolution variability of the test and reference product data should also be similar, however, a lower variability of the test product may be acceptable.

Evidence that the statistical software has been validated should also be provided.

A clear description and explanation of the steps taken in the application of the procedure should be provided, with appropriate summary tables.

5.2.1.2.2.2 Request For Biowaiver

Omission of BE studies be justified. Generally BE studies are not necessary if a product fulfils one or more of the following conditions: The following dosage forms are exempted from bioequivalence study requirements:

a) The product is a solution intended solely for intravenous administration.
b) The product is to be parenterally or orally administered as a solution.
c) The product is an oral dosage form which is not intended to be absorbed (e.g. Antacid, Radioopaque Contrast Media etc)
d) The product is an oral solution, syrup, or other similarly solubilised form;
e) The product is a solution intended for ophthalmic or otic administration.
f) The product is an inhalant volatile anesthetic solution, Inhalation and nasal preparations
g) 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
h) Gases
i) 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.
j) Powders for reconstitution as a solution and the solution meets the criteria indicated in (i) above.

5.2.1.2.2.2.1 Choice of Reference Product

This note is intended to provide applicants with some additional guidance and clarification on existing guidance documents with respect to selecting an appropriate reference product for a bioequivalence study conducted with a generic product for submission to the PPB. The following should be considered when selecting a reference product:

- The applicant should select and purchase the innovator pharmaceutical products approved in ICH - and other well regulated markets (such as Australia, Canada, Switzerland)
- The applicant should choose from the WHO comparator product list or FDA Reference Product List.
- In case of any clarification the applicant can request PPB for guidance on the choice of reference product.

Reference: http://apps.who.int/prequal/info_applicants/Guidelines/ComparatorProducts_Notes.pdf

5.2.1.2.2.2.2 General notes on Biopharmaceutics Classification System (BCS)-based biowaiver applications

In this guideline biowaivers based on the Biopharmaceutics Classification System (BCS) are intended only to investigate bioequivalence and do not apply to other bioavailability or pharmacokinetic studies.

In principle, BCS Class I (highly soluble and highly permeable) active pharmaceutical ingredients (APIs) have been identified to be eligible for the BCS-based biowaiver approach.

Until further notice, *in vivo* bioequivalence studies are required for invited monocomponent and fixed-dose combination products containing other APIs.

The information presented in this guideline is based on recommendations of the:

- WHO, as described in the "Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability". In: *Fortieth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Geneva, World Health Organization. WHO Technical Report Series, No. 937, 2006, Annex 7
- US-FDA, as described in "Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, 2000", available at: http://www.fda.gov/cder/Guidance/3618fnl.pdf
- EMEA, as described in "Guideline On The Investigation Of Bioequivalence 2010", available at: http://www.ema.europa.eu/pdfs/human/qwp/140198enrev1fin.pdf

BCS-based biowaivers are applicable for immediate-release solid oral dosage formulations containing one or more of the API(s) mentioned above if the required data ensure the similarity of the submitted pharmaceutical product and the appropriate comparator product.

Comparator products used in BCS-biowaiver applications should be selected from comparator products recommended by PPB. Use of any other comparator has to be duly justified by the Applicant.

Biowaiver-based dossiers should contain relevant information and data as outlined in the following paragraphs:

5.2.1.2.2.2.3 Comparator product suitability

Identification by PPB of an API to be eligible for a BCS-based biowaiver application is made purely on the solubility, permeability, safety and related properties of the API (Class 1 or Class 3). It does not imply that the recommended comparator product(s) will be rapidly dissolving in case of Class 1 APIs (or very rapidly dissolving in case of Class 3 API), which is a requirement for BCS based biowaiver studies. The applicant must thus ensure that the recommended comparator(s) is indeed suitable for a BCS based-biowaiver application before product development.

Note that rapidly dissolving (or very rapidly dissolving) properties of a product are not required for *in vivo* bioequivalence studies. Thus, though a listed comparator product may not be suitable for BCS-based biowaiver purposes, it is still suitable for *in vivo* bioequivalence studies.

5.2.1.2.2.2.4 Test and comparator products

It is considered to be a significant asset to a biowaiver application if the submitted (test) product contains similar amounts of the same excipients as the comparator product. Information related to this issue is usually available from public sources of stringent drug regulatory authorities. Critical excipients (*e.g.*, mannitol, sorbitol, surfactants) should be used with care, and if present, should not differ qualitatively and quantitatively between the products. As a general rule the test product should be formulated with well known excipients, in usual amounts, having no relevant impact on absorption processes.

The sameness of the manufacturing method and the quality of the test product should be demonstrated in the relevant sections of the quality part of the dossier.

The drug content or potency of the comparator product should be close to the label claim, and the difference in drug content or potency between the test and comparator products should be less than 5%.

It is recommended that samples of the test product be taken from batches of industrial scale. However, when this is not possible, a batch of 1/10 or larger of the expected full production batch, or 100 000 units, whichever is greater, can also be used as the test product, provided these batches are the same as the production batches in manufacturing method, quality and composition.

5.2.1.3 Other possible study(ies) types done to support efficacy and safety of the product

5.3 SAFETY AND RESIDUES DOCUMENTATION (FOR VETERINARY PRODUCTS ONLY)

5.3.1 Requirements for Animal Safety

5.3.1.1 Laboratory Animal Studies

Laboratory animal studies will normally be required for new chemical entities proposed for use as veterinary drugs. The information available in the published scientific literature may be accepted in lieu of studies outlined in this section. For the purpose of this guideline, these studies are required to determine potential toxic effects for the target animal species.

The basic toxicity data obtained in laboratory animals complement the data required to support the safety of a new drug in the target animal species. Depending on the intended route(s) of administration of the drug for the target animal species, the toxicity studies may be conducted by oral and/or parenteral routes of administration of drugs. The laboratory animal toxicity studies in general may be classified as acute, subchronic or chronic.

Due regard should be given to the welfare of the study animals. The use of animals for research and testing should conform to the rigorous ethical standards that are compatible with the goals of science for benefiting humans or animals. Those using animals should employ the most humane methods on the smallest number of appropriate animals required to obtain valid information. For standards for use and care of animals a reference may be made to the Guide to the Care and Use of Experimental Animals[1].

5.3.1.2 Target Animal Safety Studies

The objectives of these studies are to document: signs and effects associated with the toxicity of the new drug for the test species and its organs, tissues and functions; minimum toxic dose; maximum no-toxic-effect dose; and margin of safety. The data required for the safety in the intended target animal species may vary according to the nature of the basic toxicological data, the intended use of the proposed drug and the intended use of the target animal. The basic toxicology data are generally obtained from studies in laboratory animals. The data to establish safety of the proposed drug to the intended target animal species are obtained from the studies conducted in the target animal species. For the design and conduct of these studies a reference may be made to the Target Animal Safety Guidelines for New Animal Drugs[2].

5.3.2 Requirements for Human Safety

This Part pertains to the drugs used in food-producing animals. However, basic toxicity data obtained in laboratory animals are used to complement the data required to support the safety of the drug residues in food-producing animals. Under certain circumstances, the microbiological safety assessment may be required for veterinary antimicrobial products intended for use in non-food-producing animals.
Before a new drug intended to be used in food-producing animals can be sold in Kenya, manufacturers are required by law to submit scientific evidence demonstrating that the drug has been carefully assessed for the safety of drug residues in meat and other food products intended for human consumption. Microbiological safety assessment is also considered as a key aspect of the requirements for human safety of veterinary antimicrobials.

5.3.2.1 Laboratory Animal Toxicity Studies

Toxicity studies are used to determine toxic effects of veterinary drugs and/or their metabolites in laboratory animal species, usually rodents and non-rodents (e.g., dogs), so that adequate extrapolations can be made to estimate the potential risks of the residues of veterinary drugs for consumers ingesting foods of animal origin. All laboratory animal toxicity studies, except for tests of mutagenicity, submitted in support of human safety for use in food-producing animals are conducted using the oral route of administration. Data generated under the toxicity studies are used to establish a no observable effect level (NOEL) in the most sensitive species/strain. The established NOEL is then used to calculate an Acceptable Daily Intake for the specific drug and/or its metabolites by using an appropriate safety factor.

It is recommended that all toxicity studies be conducted in accordance with the guidelines and Good Laboratory Practice (GLP) as approved by the OECD (website: http://www.oecd.org).

Specific requirements for toxicity studies may vary from one drug to another depending on the class of veterinary drug and the extent of its proposed use.

5.3.2.2 Microbiological Safety Studies

In this section of the Human Safety Requirements, information is provided regarding the data requirements expected for demonstrating the microbiological safety of a drug product. This section pertains to antimicrobial drug products as well as products containing bacteria, for example, direct-fed microbial products.

5.3.2.2 Veterinary Antimicrobial Products

This section pertains to antimicrobial drug products (including antibacterials, antiparasitics and antivirals). However, information in this guidance is often targeted to antibacterial products. Sponsors submitting applications for other antimicrobial products may wish to consult with the Directorate for the specific requirements for their submission.

The impact of the use of antimicrobial products in food-producing animals on the development and the potential for enrichment and dissemination of antimicrobial resistant human bacterial pathogens is considered one of the principal aspects of the human safety review.

The objective of this guidance is for the sponsor to provide information necessary for assessing the potential impact of the use of veterinary antimicrobial products on the development of antimicrobial resistance in bacteria of animal origin, which may affect antimicrobial therapy in veterinary and human medicine. One of the recommendations of the *Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance and Human Health*[3] is to conduct risk-based evaluation of the potential human health effects of all uses of antimicrobials in food-producing animals. This guidance document emphasizes a preliminary risk analysis approach and outlines the data requirements to evaluate the potential for the development of bacterial resistance or cross-resistance to veterinary antimicrobial products as it might occur in the intended species, under the proposed conditions of use of the product as well as the potential for transfer of resistant bacteria or resistance determinants to humans.

5.3.2.4 Residue (Chemistry) Studies

This Part describes the absorption of the test substance after administration to animals as well as the Absorption, Distribution, Metabolism and Excretion, ADME, patterns of the test substance. The extent and duration of persistence of residues of a veterinary drug or its metabolites in edible tissues of treated animals or food products obtained from them determines the withdrawal period (withholding time for milk) needed for the residues to fall below the Maximum Residue Limit (MRL).
The summary of the residue-related studies, providing factual, concise descriptions of the test results.

REFERENCES

1. Guide to Care and Use of Experimental Animals, CCAC, 1993. (Website: http://www.ccac.ca)
2. Target Animal Safety Guidelines for New Animal Drugs. Office of New Animal Drug Evaluation. Centre for Veterinary Medicine, Food and Drug Administration, Rockville , MD 20855 , USA . 2001.
3. Uses of Antimicrobials in Food Producing Animals. Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance and Human Health, 2002. (http://www.hc-sc.gc.ca/dhp-mps/pubs/vet/amr-ram_final_report-rapport_06-27_cp-pc-eng.php
4. http://www.hc-sc.gc.ca/dhp-mps/vet/legislation/guide-ld/vdd_nds_guide-eng.php#7

DECLARATION BY AN APPLICANT

The declaration must be signed, dated and authenticated by an Official stamp. No Applications will be evaluated without authenticated declaration.

ANNEX

ANNEX I: APPLICATION FOR REGISTRATION OF A PHARMACEUTICAL PRODUCT (attached separately)

ANNEX II: MODEL STABILITY REPORT FOR ACTIVE PHARMACEUTICAL INGREDIENTS (APIs)

Prepared by: ..... Approved by: .....

Date: .....

Model Stability Report of ..... <Active Pharmaceutical Ingredient>

Approved INN name:

1. BATCHES TESTED

Batch number			
Date of manufacture			
Site of manufacture			
Batch size (kg)			
Primary packing materials			
Date of initial analysis			

Note: The batches to be sampled should be representative of the manufacturing synthesis process and should be manufactured from different batches of key intermediates.

2. GENERAL INFORMATION

- Structure
- Chemical name(s)
- Other non-proprietary name(s), e.g., national name, United States Adopted Name (USAN), Japanese Accepted Name (JAN); British Approved Name (BAN)
- Chemical Abstracts Service (CAS) registry number

3. CONTAINER/CLOSURE SYSTEM

A description of the container/closure system(s) should be provided, including the identity of materials of construction of each primary packaging component, and their specifications. The specifications should include description and identification.

4. LITERATURE AND SUPPORTING DATA

Before stability studies are initiated, information on the stability of the active pharmaceutical ingredient (API) should be sought, collected and analyzed. Published decomposition process and degradability of the API and the finished pharmaceutical products (FPP) should be referred to.

Stability data can be presented on laboratory- and pilot-scale batches and on synthesis routes other than those proposed for marketing.

Note: Literature data, if available, should be scrutinized, sometimes experimentally verified, and completed with information on polymorphism, particle size, hygroscopicity, etc., if applicable.

5. STABILITY-INDICATING ANALYTICAL METHODS

Make reference to the release specification number containing the description of validated, stability-indicating methods. The accuracy as well as the precision (standard deviations) of the methods should be recorded. The tests for impurities and degradants should be validated to demonstrate that they are specific to the API being examined and are of adequate sensitivity

6. TESTING PLAN

Storage condition	Storage time (months)								
	0	3	6	12	18	24	36	48	60
Accelerated: 40±2°C/75±5 % RH	X	X	X						
Long term*****: 30±2°C/65±5 % RH	X	X	X	X	X	X	X	X	X
Long term (2): 25±2°C/60±5 % RH	To be conducted only if the API is not stable at 30°C								

***** The long term studies should cover the whole retest period, which is not necessarily five (5) years.

A significant change is considered to have occurred if:

- The assay value shows a 5% decrease as compared with the initial assay value of a batch;
- Any specified degradation product is present in amounts greater than its specification limit;
- The specifications for appearance and physical properties, e.g. color, are no longer met.

7. TEST PARAMETERS

7.1 Chemical characteristics [assay, contents of impurities and degradants].

7.2 Physical characteristics [e.g. appearance including possible change in color, moisture content as well as polymorphs if applicable].

7.3 Photostability testing should be conducted on at least one primary batch of the API.

7.4 Microbiological attributes (total microbial count and absence of pathogens, every year) when the API is intended to be used in a parenteral dosage form.

8. OTHER REQUIREMENTS

8.1 A stability report must be prepared giving details of the study results and conclusions. The results should be presented as both a table and a graph.

8.2 The stability of a given API, and therefore the proposed retest period and storage conditions, must be proposed on the basis of these results.

8.3 Where the data show so little degradation and so little variability that it is apparent from looking at the data that the requested retest period will be granted, it is normally unnecessary to go through the formal statistical analysis; providing a justification for the omission should be sufficient.

8.4 An approach for analyzing data of 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.

8.5 Storage conditions recommended on the basis of stability studies should be prominently indicated on the label.

8.6 Once the API supplier has been approved, additional stability studies are required whenever major modifications are made to the manufacturing synthesis process, packaging materials or methods.

9. CONCLUSIONS

The obtained stability data support a proposed retest date of ... months.

Storage conditions and retest date approved by the national Drug Regulatory Authority on the basis of stability studies should be prominently indicated on the label.

Contact person in Applicant Company

Name: Position in the company:

Postal address: Physical address:

Telephone number: Fax number: E-mail address:

ANNEX III: MODEL STABILITY REPORT FOR FINISHED PHARMACEUTICAL PRODUCTS

Prepared by: .....

Approved by: .....

Date: .....

Model Stability Report of .....mg Capsules/Tablets

Approved generic name, if different from the name in the title above:

1. BATCHES TESTED

Batch number			
Date of manufacture			
Site of manufacture			
Batch size (kg)			
Batch size (number of units)			
Primary packing materials			
Date of initial analysis			
Batch number of the active pharmaceutical ingredient (API)			

2. UNIT COMPOSITION OF A CAPSULE/TABLET

3. CONTAINER/CLOSURE SYSTEM

Give a detailed description of the container/closure system(s), including any liner or wadding, and provide details of the composition of each component. Describe other (e.g. outer) packaging, and state what materials they are made from. Provide the specifications for any part of the container/closure system(s), which comes into contact with the product or is protective.

4. LITERATURE AND SUPPORTING DATA

Published decomposition process and degradability of the API and the finished pharmaceutical products (FPP) revealed that……...

Development formulations and stress tests in open systems (in particular, 100% RH and light) showed that ……...

5. STABILITY-INDICATING ANALYTICAL METHODS

Make reference to release and at-the-end of shelf life specification numbers containing the description of validated, stability-indicating methods.

The accuracy as well as the precision of the method is … standard deviations.

The tests for impurities and degradants have been validated (validation report is attached).

6. TEST RESULTS

Batch No.:

Container:

Chemical data

Initial values			
Storage condition	**Assay (mg)**	**Degradant 1 (%)**	**Degradant 2 (%)**
3 months, 40±2 °C / 75±5 %RH 3 months, 30±2°C / 65±5 % RH			
6 months, 40±2 °C / 75±5 %RH 6 months, 30±2°C / 65±5 % RH			
12 months, 30±2°C / 65±5 % RH			
18 months, 30±2°C / 65±5 % RH			
24 months, 30±2°C / 65±5 % RH			
36 months, 30±2°C / 65±5 % RH			
48 months, 30±2°C / 65±5 % RH			
60 months, 30±2°C / 65±5 % RH			

Batch No.:

Container:

Physical data

Initial values			
Storage condition	**Appearance**	**Dissolution rate,…min., %**	**LOD**
3 months, 40±2 °C / 75±5 %RH 3 months, 30±2°C / 65±5 % RH			
6 months, 40±2 °C / 75±5 %RH 6 months, 30±2°C / 65±5 % RH			
12 months, 30±2°C / 65±5 % RH			
18 months, 30±2°C / 65±5 % RH			
24 months, 30±2°C / 65±5 % RH			
36 months, 30±2°C / 65±5 % RH			
48 months, 30±2°C / 65±5 % RH			
60 months, 30±2°C / 65±5 % RH			

Note: change headings and add tables, as necessary.

Batch No.:

Container:

Microbiological attributes

Initial values		
Storage condition	Total microbial count	Pathogen microbes
3 months, 40±2 °C / 75±5 %RH 3 months, 30±2°C / 65±5 % RH		
6 months, 40±2 °C / 75±5 %RH 6 months, 30±2°C / 65±5 % RH		
12 months, 30±2°C / 65±5 % RH		
18 months, 30±2°C / 65±5 % RH		
24 months, 30±2°C / 65±5 % RH		
36 months, 30±2°C / 65±5 % RH		
48 months, 30±2°C / 65±5 % RH		
60 months, 30±2°C / 65±5 % RH		

7. ANALYSIS OF RESULTS

7.1 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 formal statistical analysis; providing a justification for the omission should be sufficient.

7.2 If data of a quantitative attribute that have changed significantly during the stability tests, present them in a graph and 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.

8. CONCLUSIONS

The obtained stability data support a proposed shelf life of …….... months.

Note: Storage conditions approved by the Pharmacy and Poisons Board on the basis of stability studies should be prominently indicated on the label.

Contact person in Applicant Company

Name:

Position in company:

Postal address:

Telephone number: Fax number:

E-mail address.

ANNEX IV: SUMMARY OF PRODUCT CHARACTERISTICS

Propose a copy of the Summary of Product Characteristics (SPC) aimed at medical practitioners and other health professionals using the format outlined below. The SPC is an essential part of drug registration and it can only be changed with the consent of PPB.

Applicants may present SPCs for different strengths in one document, clearly indicating with shaded titles the strength or presentation to which alternative text elements refer.

However, a separate SPC per strength and per pharmaceutical form, containing all pack-sizes related to the strength and pharmaceutical form concerned will have to be provided by the applicant

Standard statements are given in the template, which must be used whenever they are applicable. If the applicant needs to deviate from these statements to accommodate product-specific requirements, alternative or additional statements will be considered on a case-by-case basis.

Bracketing convention: <text>: standard text statement to be selected or deleted as appropriate

Reference: *"Summary of Product Characteristics" published on the Website of the European Commission in the Notice to Applicants, Volume 2C: http://pharmacos.eudra.org/F2/eudralex/vol-2/home.htm*

1. Name of the medicinal product

1.1 (Invented) name of the medicinal product

State the name under which the product will be marketed in Kenya. In case of 'generic' products, the International Non– Proprietary Name (INN) in block letters and a trade mark name in small letters if any.

In those sections of the SPC in which full information on the name of the medicinal product is specifically required, the name should be followed by both the strength and the pharmaceutical form.

However, when otherwise referring to the medicinal product throughout the 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.

1.2 Strength

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

1.3 Pharmaceutical form

The pharmaceutical form should be described by the standard term using plural form if appropriate (e.g. tablets). If an appropriate standard term does not exist, a new term may be constructed from a combination of standard terms. No reference should be made to the route of administration or to the container unless these elements are part of the standard term or where there are identical products, which may be distinguished only by reference to the container.

2. Qualitative and quantitative composition

Provide full details of the qualitative and quantitative composition per unit dosage form in terms of the active substances and excipients, knowledge of which is essential for proper administration of the medicinal product. The usual common name or chemical description shall be used.

Provide a full list of excipients, see section 6.1

Reference: *"Guideline on excipients" published on the Website of the European Commission in the Notice to Applicants, Volume 3B http://pharmacos.eudra.org/F2/eudralex/vol-3/home.htm.*

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

Qualitative declaration

The active substance should be declared by its recommended INN, accompanied by its salt or hydrate form if relevant, or the Pharmacopoeial name if that name represents an established name. If no INN exists, the Pharmacopoeial name should be used or if the substance is not in the pharmacopoeia, the usual common name should be used. In the absence of a common name, the exact scientific designation should be given. Substances not having an exact scientific designation should be described by a statement on how and from what they were prepared. References to the pharmacopoeial quality should not be included.

When the medicinal product is a radiopharmaceutical kit, the qualitative declaration should clearly indicate that the radioisotope is not part of the kit.

Quantitative declaration
The quantity of the active substance must 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 must be related to the declaration of strength in section 1.

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 entity (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 manufacture of the finished product, the quantity of the active entity should be stated, with a reference to the *in situ* formation of the salt.

In the case of established active substances in medicinal 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.*

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 entity is an active substance of an already approved medicinal product, the quantitative composition should also be stated in terms of the quantity of this active entity.

Oral powders for solution or suspension
The quantity should be stated per unit dose if the product is a single-dose preparation or otherwise per unit dose volume after reconstitution; a reference to the molar concentration may also be appropriate in some cases.

Parenterals excluding powders for reconstitution

For single-dose parenterals, where the total contents of the container are given in a single dose ('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.

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.

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.

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'.

Multidose solid or semi-solid products

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

Biological products

In the case of normal immunoglobulins, the IgG subclass distribution should be stated.
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.
The nature of any cellular system(s) used for production, and if relevant the use of recombinant DNA technology, including the use of the expression 'produced in XXX cells <by recombinant DNA technology>'should be mentioned in the SPC, in a pattern as set by the following examples:
• 'produced in human diploid (MRC-5) cells',
• 'produced in *Escherichia coli* cells by recombinant DNA technology',
• 'produced in chick-embryo cells' and
• 'derived from human plasma donors'.

3. Pharmaceutical form

State clearly the pharmaceutical dosage form of the product, e.g. tablets, capsules, injection, etc. Any descriptive terms to give an indication of the exact type of dosage form should also be included e.g. film-coated tablets, enteric-coated tablets, hard-gelatin capsules, soft-gelatin capsules, oily injection etc.

The visual and physical characteristics of the product should also be stated, including where applicable: shape, size, superficial markings for identification purposes, colour, odour, taste, pH, osmolarity, etc as required e.g.

'*Tablet*
White, circular flat bevelled-edge tablets marked '100' on one side'

In case of tablets designed with a score line, information should be given whether or not reproducible dividing of the tablets has been shown. e.g. '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'.

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 section 4.2.

4. Clinical particulars

4.1 Therapeutic indications

State briefly recommended therapeutic use(s) of the product. Indications should be specific; phrases such as 'associated conditions' or 'allied diseases' should be avoided.

Specify, if appropriate <This medicinal product is for diagnostic use only.>

If applicable, results of clinical trials to appear under section 5.1.

4.2 Posology and method of administration

State the dose (normal dose, dose range), dosage schedule (frequency, duration) and route of administration appropriate for each therapeutic indication. Dosages for adults, children, should be stated clearly. Dosage adjustments for special conditions, e.g. renal, hepatic, cardiac, nutritional insufficiencies, where relevant, should be stated. Distinction should be made between therapeutic and prophylactic doses and between dosages for different clinical uses where applicable.

In case of restricted medical prescription start this section by specifying the conditions.

Method of administration: directions for proper use by healthcare professionals or by the patient. Further practical details for the patient can be included in the package leaflet, e.g. in the case of inhalers, subcutaneous self-injection.

Instructions for preparation are to be placed under section 6.6 and cross-referenced here.

4.3 Contraindications

Outline situations where patients should never or generally not be treated with the product and in rare cases where the product should not be used.

State any 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

State briefly the precautions and warnings that should be taken when or before using the product. Describe the conditions under which the product may be recommended for use in subgroups of patients at risk provided that the special conditions of use are fulfilled. Emphasis should be given to a serious risk by underlining the seriousness (i.e. possibility of death). State also any special pharmaceutical precautions e.g. incompatible diluents, additives etc.

4.5 Interaction with other medicinal products and other forms of interaction

State briefly the interactions of the product with other drugs, food or any other substances and where applicable the mechanism of interaction.

<No interaction studies have been performed.>

<Interaction studies have only been performed in adults.>

4.6 Pregnancy and lactation

Provide information on the use of the product in pregnant women and lactating mothers. Results from reproduction toxicology should be included under section 5.3 below and cross-referenced here, if necessary.

4.7 Effects on ability to drive and use machines

Provide information on the effects of the product on the ability to drive and operate machines. Studies performed on the same should be provided or cross referenced, where applicable.

Describe effects where applicable: <<no> or negligible> influence> <minor or 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

State the side effects and adverse reactions of the product as per the MedDRA frequency convention and system organ class database.

Within each frequency grouping, undesirable effects should be presented in order of decreasing seriousness.

4.9 Overdose

Describe symptoms of over-dosage or poisoning and the recommended treatment, emergency procedures and antidotes (if available).

<No case of overdose has been reported.>

5. Pharmacological properties

5.1 Pharmacodynamic properties

Give a concise summary of the pharmacodynamic properties of the drug(s) relevant to the proposed indications. Include the Pharmacotherapeutic group: {group *[lowest available level]*}, ATC code: {code}

5.2 Pharmacokinetic properties

Give a concise summary of the pharmacokinetic properties (i.e. absorption, distribution, metabolism and excretion) of the drug(s).

5.3 Preclinical safety data

Describe the safety profile of the product in relation to single dose toxicity, repeated dose toxicity, carcinogenicity, genotoxicity, reproduction, toxicity and dependence liability.

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 should also be outlined.

<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.>

<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

List each excipients on a separate line according to the different parts of the product.

6.2 Incompatibilities

Provide information on incompatibilities of the product with other medicinal products. (e.g. mixing of medicinal products during administration).

<Not applicable.> *[if appropriate, e.g. for solid oral pharmaceutical forms.]*

<In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.> *[e.g. for parenterals.]*

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

6.3 Shelf life

Provide information on the finished product shelf life and on the in-use stability after 1st opening and/or reconstitution/dilution. Only one overall shelf life for the finished product should be given even if different components of the product may have a different shelf life (e.g. powder & solvent).

These should be stated in the following format:

<0 month> <6 months> <1 year> <18 months> <2 years> <30 months>

6.4 Special precautions for storage

State the general storage conditions of the finished product should appear here, together with a cross-reference to section 6.3 where appropriate: <For storage conditions of the <reconstituted> <diluted> medicinal product,see section 6.3>

State briefly:

(a) The recommended storage conditions (temperature, humidity, light, etc.) as established by stability studies. The storage temperature must be stated in figures e.g. Store below 30°c protected from light (see also 3.10.12 below for Core Storage Statements).

(b) Any special user instructions, e.g. dilution, reconstitution and storage and shelf life after reconstitution, etc.

6.5 Nature and contents of container

State briefly the type(s) of packing and pack size(s) being applied for registration. The pack sizes declared here should correspond with the samples submitted.

6.6 Special precautions for disposal

Provide practical instructions for preparation and handling of the product including disposal of the medicinal product and waste materials derived from the used medicinal product.

<No special requirements.>

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

7 Registrant

State the name and address of marketing authorization holder including telephone, fax number and e-mail.

8 Manufacturer

State the name and physical address of the site(s) of manufacture of the product including telephone, fax number and e-mail.

9 Date of revision of the text

To be stated at the time of printing once a change to the SPC has been approved.

{MM/YYYY}

10 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.

11 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.

GLOSSARY

In the context of this guideline, the following words/phrases are defined as follows.

Active Pharmaceutical Ingredient (API): Means a substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a therapeutically active compound (ingredient).

Applicant: A person who owns a formula or trademark of a product, who may be a manufacturer or a person to whose order and specifications the product is manufactured and who shall be the registration holder and have the primary responsibility of the product on the Kenyan market.

Bio-equivalence: Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or alternatives and their bioavailabilities (rate and extent of availability), after administration in the same molar dose, are similar to such a degree that their effects can be expected to be essentially the same.

Board: Means the Pharmacy and Poisons Board, or its acronym "PPB" established under Pharmacy and Poisons Act, CAP 244, section 3.

Composition: Composition in relation to a medicinal product means the ingredients of which it consists, proportions, degree of strength, quality and purity in which those ingredients are contained.

Container labelling: Means all information that appears on any part of a container, including that on any outer packaging such as a carton.

Container: Means a bottle, jar, box, packet, sachet or other receptacle which contains or is to contain in it, not being a capsule or other article in which the product is or is to be administered or consumed, and where any such receptacle is or is to be contained in another receptacle, includes the former but does not include the latter receptacle.

Drug Master File**:** A drug master file (DMF) is a master file that provides a full set of data on an API. In some countries, the term may also comprise data on an excipient or a component of a product such as a container.

Drug, medicine or pharmaceutical product: The Pharmacy and Poisons (Registration of Drugs) Rules, defines "drug" means a substance or mixture of substances which can be used for any of the following purposes-

(a) treating, preventing or alleviating symptoms of disease

(b) diagnosing disease or ascertaining the existence, degree or extent of a physiological condition: or

(c) otherwise preventing or interfering with the normal operation of a physiological function, whether permanently or temporarily and whether by way of terminating, reducing, postponing or increasing or accelerating the operation of that function.

Established active pharmaceutical ingredient: Means APIs which are subject of the current pharmacopoeias or those well documented in the literature and generally recognized as safe and effective for use as a medicine.

Established Generics: Means FPPs which are subject of the current pharmacopoeias or those well documented in the literature and generally recognized as safe and effective for use as a medicine.

Excipient: Means any component of a finished dosage form which has no therapeutic value.

Finished Pharmaceutical Product (FPP): Means a product that has undergone all stages of production, including packaging in its final container and labelling

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

Generic (multisource) product(s): Means products that are pharmaceutical equivalents or alternatives to innovator or reference products and which are intended to be therapeutically equivalent and can therefore be used interchangeably with the innovator or reference product. It is pharmaceutical product usually intended to be interchangeable with the innovator product, which is usually manufactured without a licence from the innovator company and marketed after the expiry of patent or other exclusivity rights.

Innovator pharmaceutical product: Means a pharmaceutical product, which was first authorized for marketing (normally as a patented product) on the basis of documentation of efficacy, safety and quality (according to the requirements at the time of authorization).

Interchangeability: An interchangeable pharmaceutical product is one that is therapeutically equivalent to an innovator (reference) product.

Label: Means any tag, brand, mark, pictorial or other descriptive matter, written, printed, stenciled, marked, embossed or impressed on or attached to a container of any drug

Manufacture (manufacturing): Means all operations of purchase of materials and products, production, quality control, release, storage, shipment of finished products and the related controls.

Manufacturer: Means a person or firm that is engaged in the manufacture of product(s).

Marketing authorization (registration) holder: Means an official authorization or registration of a product by PPB for the purpose of marketing in Kenya after evaluation for safety, efficacy and quality.

New active pharmaceutical ingredient: Means a drug (active ingredient), including its salts, esters, derivatives, etc. or biological agent, which is not a subject of current pharmacopoeias.

New combination: Means a product containing drugs in combinations (qualitative content and/or proportions) different from those products that are subject of current pharmacopoeias.

***New pharmaceutical product*:** A pharmaceutical product that contains a new API, a new combination of marketed APIs or a new multisource (generic) product.

Pharmaceutical alternatives: Two or more medicinal products are said to be pharmaceutical alternatives if they contain the same active ingredients, but which may differ in salt, esters, dosage forms, strength and/ or route of administration.

Pharmaceutical equivalents: Products are pharmaceutical equivalents means products that contain the same amount of the same active substance(s) in the same dosage form; if they meet the same or comparable standard; and if they are intended to be administered by the same route.

Pharmacopoeia: Means a current edition of the British Pharmacopoeia, European Pharmacopoeia, United States Pharmacopoeia, International Pharmacopoeia and Japanese Pharmacopoeia.

Pilot Batch: The batch should correspond to at least 10% of the future industrial scale batch i.e. such that the multiplication factor for scale-up does not exceed 10. For oral solid dosage forms this size should be at least 10% or 100,000 units whichever is greater unless otherwise justified

Specifications – expiry check or shelf life: Means the combination of physical, chemical, biological and microbiological test requirements that an active ingredient must meet up to its retest date or a drug product must meet during its shelf life.

Specifications – release: Means the combination of physical, chemical, biological and microbiological test requirements that determine whether a drug product is suitable for release at the time of its manufacture.

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

Therapeutic equivalence*:* Two pharmaceutical products are therapeutically equivalent if they are pharmaceutically equivalent and, after administration in the same molar dose, their effects with respect to both efficacy and safety essentially the same, as determined from appropriate bioequivalence, pharmacodynamic, clinical or *in vitro* studies.

Variation: Means a change to any aspect of a pharmaceutical product, including but not limited to a change to formulation, method and site of manufacture, specifications for the finished product and ingredients, container and container labelling and product information.

----------END----------