RWANDA FDA
Rwanda Food and Drugs Authority

GUIDELINES ON SUBMISSION OF DOCUMENTATION FOR REGISTRATION OF HUMAN MEDICINAL PRODUCTS

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FOREWORD

Rwanda Food and Drugs Authority (Rwanda FDA) is a regulatory body established by the Law N° 003/2018 of 09/02/2018. One of the functions of Rwanda FDA is to regulate matters related to quality, safety and efficacy of human medicinal products in order to protect public health by increasing access and availability of essential medicines.

Considering the provisions of the technical Regulations N^{o} CBD/TRG/010 Governing the registration of human medicinal products especially in its articles 6, 7, 8, 9, 12 and 32, the authority has to issue *Guidelines N^{o} DHT/GDL/001 on submission of documentation for registration of human medicinal products*.

Rwanda FDA adopted the Common Technical Document (CTD) Guidelines on Submission of Documentation for registration of human medicinal products. These guidelines have been developed to provide guidance to the applicants and the Authority in managing applications for registration of human medicinal products. These guidelines were developed in reference to the existing Ministry of Health (MOH) guidelines on submission of documentation for registration of Human Pharmaceutical Products which were domesticated based on Compendium of Medicines Evaluation and Registration for Medicines Regulation Harmonization in the East African Community, World Health Organization (WHO) and the International Conference on Harmonization of Technical Requirements for Registration of Medicines for Human Use (ICH) and other available literature.

The Authority acknowledges all the efforts of key stakeholders who participated in the development and validation of these guidelines.

Dr. Charles KARANGWA
Ag. Director General

GUIDELINES DEVELOPMENT HISTORY

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TABLE OF CONTENT

ABBREVIATIONS AND ACRONYMS

API	Active Pharmaceutical Ingredient
APIMF	Active Pharmaceutical Ingredient Master File
BA	Bioavailability
BE	Bioequivalance
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CTD	Common Technical Document
EAC	East African Community
EDQM	European Directorate for the Quality of Medicines
EU	European Union
FPP	Finished Pharmaceutical Product
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HDPE	High Density Polyethylene
ICH	International Conference on Harmonization
INN	International Non-proprietary Name
PD	Product Dossier
PHIS	Pharmaceutical Health Information System
PI	Product Information
Rwanda FDA	Rwanda Food and Drugs Authority
QIS	Quality Information Summary
QOS	Quality Overall Summary
QOS-PD	Quality Overall Summary- Product Dossier
SmPC	Summary of Product Characteristics
SRAs	Stringent Regulatory Authorities
WLAs	WHO Listed Authorities

DEFINITIONS

The definitions provided below apply to the words and phrases used in these guidelines. The following definitions are provided to facilitate interpretation of the guidelines. Other terminologies can be found in the Rwanda FDA glossary of terms (***Refer to the Guidance N^{o} DHT/GDL/010H)***.

Active pharmaceutical ingredient (API)

An active pharmaceutical ingredient is any component that provides pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or animals.

Active Pharmaceutical Ingredient (API) starting material

A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API.

Applicant

An applicant is a person who applies for registration of a human medicinal product to Rwanda FDA, who must be the owner of the product. He may be a manufacturer or a person to whose order and specifications, the product is manufactured.

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

Authority

Means the Rwanda Food and Drugs Authority or its acronym "Rwanda FDA", established under the article 2 of the Law No. 003/2018 of 09/02/2018.

Authorized person

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

Batch (or lot*)*

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

Batch number (or lot number)

A unique number or combination of numbers or symbols allocated to a lot or a batch by the manufacturer

Manufacturing Batch records

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

Bulk product

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

Calibration

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

Certification

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

Challenge tests/worst case

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

Clean area

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

Commitment batches

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

Comparator product

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

Critical process

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

Cross-contamination

Contamination of a starting material, intermediate product, or finished product with another starting material or product during production.

Existing API

An API that is not considered a new active substance, which has been previously approved through a finished product by a stringent regulatory authority.

Finished pharmaceutical product (FPP)

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

Generic medicinal product

Is a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and which is bioequivalent with the reference medicinal product. Detailed information can be found in the Rwanda FDA glossary of terms.

Innovator medicinal product

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

In-process control

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

Installation qualification

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

Intermediate product

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

Large-volume parenterals

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

Local Technical Representative (LTR)

Any applicant who is not resident in Rwanda shall appoint a local technical representative who must be a company incorporated in Rwanda and authorized by Rwanda FDA to deal in medicinal products and must hold a wholesale operating license. The appointment shall be notified to the Authority by submitting a letter of appointment supported by original copy of power of attorney duly notarised in country of origin,

Manufacture

All operations that involve preparation, processing, filling transforming, packaging, and repackaging and labelling of medicinal products.

Manufacturer

A manufacturer is person or a firm that is engaged in the manufacture of medicinal products. It involves operations such as production, packaging, repackaging, labelling and relabeling of pharmaceuticals.

Manufacturing process

The transformation of starting materials into finished products (drug substances or pharmaceutical dosage forms) through a single operation or a sequence of operations involving installations, personnel, documentation and environment.

Marketing authorization (product license, registration certificate)

Approval from the authority necessary to market and sell a product in Rwanda. This is a legal document that establishes the detailed composition and formulation of the product and the pharmacopoeia or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labelling and shelf-life.

Master formula

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

Master record

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

Medicinal product

Any substance, or mixture of substances manufactured, sold, or presented as capable of preventing, treating human or animal diseases and any other substance intended for administration to a human being or an animal in order to diagnose diseases, restore, correct or carry out modification of organic or mental functions. It also means products used in disinfecting premises in which food and drugs are manufactured, prepared or stored, for cleaning hospitals, equipment and farm houses.

Mock-up

A copy of the flat artwork design in full colour, providing a replica of both the outer and immediate packaging, providing a two-dimensional presentation of the packaging/ labelling of the medicine. It is also referred to as a *paper copy* or *computer generated version*.

Officially recognized pharmacopoeia (or compendium)

The official recognized pharmacopoeias by RWANDA FDA are British Pharmacopoeia (BP), European Pharmacopoeia (Ph.Eur.), The International Pharmacopoeia (Ph.Int), Japanese Pharmacopoeia (JP) and United States Pharmacopeia (USP)

On-going stability study

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

Operational qualification

Documented verification that the system or sub-system performs as intended over all anticipated operating ranges.

Packaging

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

Packaging material

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

Pharmaceutical product

Any substance capable of preventing, treating human or animal diseases and any other substance intended for administration to a human being or an animal in order to diagnose diseases, restore, correct or carry out modification of organic or mental functions. It also means products used in disinfecting premises in which food and drugs are manufactured, prepared or stored, cleaning hospitals, equipment and farm houses.

Pilot-scale batch

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

Primary batch

A batch of an API or FPP used in a stability study, from which stability data are submitted in a registration application for the purpose of establishing a retest period or shelf-life. (*WHO Glossary of Terms*)

Production

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

Production batch

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

Qualification of equipment

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

Reconciliation

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

Recovery (or blending)

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

Reprocessing

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

Revalidation

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

Specification

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

Standard operating procedure (SOP)

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

Starting material

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

Specimen

A sample of the actual printed outer and inner packaging materials and package leaflet

Stringent Regulatory Authority(SRA)/ WHO Listed Authorities (WLAs)

A regulatory Authority which is a member of the International Conference on Harmonisation (ICH) or an ICH observer, or is associated with an ICH member through a legally-binding, mutual recognition agreement.

System

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

Validation

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

Validation protocol (or plan)

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

Validation report

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

Wholesale Operating License

It is a permit issued by the Authority to the company in order to deal with pharmaceutical products.

INTRODUCTION

1.1 Background

Rwanda Food and Drugs Authority (Rwanda FDA) is established by the Law N° 003/2018 of 09/02/2018, especially in its article 8 and 9;

Considering the provisions of the technical regulations No CBD/TRG/010 of ……../…. /2020 governing the registration of human medicinal products especially in its articles 6, 7, 8, 9, 12 and 32 the Authority has issued **Guidelines No DHT/GDL/001 on submission of documentation for registration of human medicinal products.**

These guidelines provide guidance for applicants preparing a Common Technical Document (CTD) for the Registration of Medicines for Human Use for submission to Rwanda FDA. The document describes how to organize applications based on the International Conference on Harmonization (ICH) of Technical Requirements for Registration of medicines using the CTD format.

According to the CTD format, each application is a collection of documents, grouped into 5 modules. Module 1 prescribes Administrative Information and Prescribing Information requirements, which is country specific. The Summaries, Quality, Non-clinical, and Clinical modules have been described in Modules 2 to 5, respectively.

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

Information in these Modules should be presented in relevant sections.

1.2 Scope

These guidelines apply to Product dossier applications for human medicinal products containing APIs of synthetic or semi-synthetic origin. The principles in these guidelines would also apply to chemical combinations and complexes that comprise more than one active ingredient including fixed dose combinations (FDC).

More details on the scientific principles applicable to the assessment of FDC products is stipulated in the *Rwanda FDA guidance on registration of fixed dose combination (FDC) for human medicinal products* ***(Refer to Guidance No DHT/GDL/001I).*** Biological, biotechnological and herbal products are not covered by these guidelines.

1.3 Preparation and Presentation of Information in CTD format

The applicant shall prepare and present the product dossier information in CTD format according to the requirements as stipulated in these guidelines:

a) The application should be typed in **English**. Any document which is in any language other than English must be accompanied by a certified or notarized English translation.
b) The application must contain a complete index to the various appendices.
c) The summaries (Quality Information Summary, Quality Overall Summary, Bioequivalence Trial Information and Bio waiver Application Form) should be formatted as word document downloadable on Authority's website and the body data in PDF .
d) All pages of the application should be numbered in the style: ***page x of y***.
e) Payment of fees shall be made in accordance to regulations N^{o} CBD/TRG/004 related to regulatory services tariffs/ fees and charges. The fees are for each respective product registration excluding transfer and other charges.
f) The application should be submitted in a virus free CD-ROM or External Driver addressed to Rwanda FDA
g) The PDF documents should be in OCR (Optical Character Recognition), selectable and searchable

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

#	TYPE OF FORMULATION AND APPLICATION	APPLICATION	
		Same	**Separate**
1	Each individual dosage form of a particular medicine		**X**
2	Variations of the active pharmaceutical ingredient (API) of a Product		**X**
3	Tablets/Capsules/Suppositories/Lozenges		**X**
4	Different pack-sizes of exactly the same strength and formulation.	**X**	
5	Different strengths and formulations.		**X**
6	Uncoated and coated tablets of the same strength and formulation		**X**
7	Syrups/Liquids/Solutions (excluding parenterals) Ointments /Creams/ different container sizes of the same strength and formulation.		**X**
8	The same container size of different strengths and formulations. Ampoules and Vials and Large Volume Parenterals		**X**
9	Ampoules or single dose vials containing identical solutions of the same strength but of different volumes (i.e. resulting in different total doses).		**X**
10	Ampoules containing solutions of different strengths.		**X**
11	Ampoules and single dose vials containing e.g. dry powder, crystals of different mass	**X**	
12	Ampoules and single dose vials containing the same respective masses of e.g. dry powder, crystals.	**X**	

13	Ampoules, single dose vials, as well as pre-filled disposable syringes and cartridges containing identical solutions of the same strength and same volume of liquid.	**X**	
14	Dental cartridges containing different volumes of fluids of the same strength (provided the dose remains constant).	**X**	
15	Ampoules containing "water for injection", but of different volumes. Special ampoules of dry powder and "water for injections" contained in the same unit, but intended for mixing at the time of injection if water for injections is fully described in dossier.	**X**	
16	Ampoules containing identical solutions of different volumes used only as diluents in the reconstitution of a preparation for parenteral use.		**X**
17	Multidose vials containing different volumes of the same strength and formulation with the same dosage schedule.	**X**	
18	Multidose vials and a single dose ampoule or vial of the same formulation if the single-dose ampoule or vial corresponds to the dose indicated for the Multidose vial.	**X**	
19	Multidose vials containing dry powder of different mass of the reconstituted.	**X**	
20	An ampoule of diluents packed together with any preparation including biological medicines if diluent is fully described in dossier.	**X**	
21	Infusion solutions of different volumes and of the same formulation which are packed in containers of exactly the same type of material depending on the relevant information submitted.		**X**
22	Infusion solutions of the different volumes and of the same type of material depending on the relevant information submitted.		**X**

23	Infusion solutions of the same formulation and of the same or different volume which are packed in containers made of different types of materials.		**X**
24	A preparation, packed in plastic containers, intended to be marketed in glass containers containing the same volume and the same formulation.		**X**
25	Products with the same strength and formulation but with different colours and/or flavours.		**X**
26	Applications containing the same API(s) applying for additional indications which render the product in a different scheduling status, or different pharmacological classification, or have any other restrictions imposed other than the original application.		**X**
27	Removal of antimicrobial preservative from single dose presentation of registered vaccine that included a preservative in the original approved formulation		**X**
28	Same formulation with different proprietary names whether of the same or different applicants		**X**

1.4 Submission of application

An application for product registration for either locally manufactured or imported, shall be made in writing via a cover letter and application form dated and signed by the applicant. If the applicant is a foreign company, the applicant shall appoint a local technical representative through whom an application shall be submitted. The local agent shall be a registered wholesale company or an accredited manufacturer's representative**.**

The application should be submitted to Rwanda FDA through the authorized local technical Representative to the following address:

Director General
Rwanda Food and Drugs Authority
P. O. Box 84
Kigali- Rwanda

1.5. Officially Recognized References

The official recognized pharmacopoeias by the Authority Are British Pharmacopoeia (BP), European Pharmacopoeia (Ph.Eur.), The International Pharmacopoeia (Ph.Int), Japanese Pharmacopoeia (JP) and United States Pharmacopeia (USP). References should be cited in accordance with the current edition of compedial.

When reference is made to specifications, quality control procedures and test methods in official recognized compendia or scientific publications, full references and copies of relevant pages shall be enclosed.

All in-house processes quoted in the documentation must have been validated and appropriate references cited

1.6 Types of Product Registration Applications

For the purposes of submission of Product Dossier to Rwanda FDA, applications are classified into three categories as follows:

1. **New applications for registration:** an application for registration of product that is intended to be placed on the Rwandan market for the first time or product which was on the market without registration certificate.
2. **Renewal of product registration:** Applications for renewal of a registered product. The application shall be made at least **3** months before the expiry of existing registration.
3. **Variation of a registered product:** an application for any change in the registered products. All applications for variation to a registered product shall be made according to requirements as stipulated in the Rwanda FDA *Guidelines for Variation of Registered human medicinal products.*

1.7 Application requirements

An application for human medicinal product registration in Rwanda shall include the following:

1. Signed and dated original hard-copy of cover letter
2. Signed and dated application form for product registration
3. Proof of payment of registration fee at the time of submission
4. Two CD-ROMs containing CTD document Format in (PDF), QOS, QIS, in MS-Word
5. Two commercial samples of the FPP with CoAs

1.8. Receiving of new applications for product registration

An application consists of electronic copies, online submission or specified hard copies where applicable. The application of product registration is only received by the Authority when the payment of prescribed registration fees is made. After receiving a product registration application, a reference number is assigned to the application and it will be used in all subsequent correspondences relating to the application. An acknowledged receipt will be issued.

1.9 Rwanda FDA Dossier Assessment Procedures

After receiving the product application, Rwanda FDA shall proceed with screening of the dossier for completeness. In the event that the dossier is incomplete, it will not be scheduled for assessment and the applicant will be notified within **30** working days and requested to comply with requirements in writing.

In case of a positive outcome during the screening, the application will be scheduled for assessment according to the First in First out (FIFO) rules. Priority assessment may be granted where the product is intended for treatment of rare disease conditions through an expression of interest (EOI DHT/FMT/032) or in the case of emergency situation.

A product dossier is reviewed by two assessors to provide scientific and regulatory oversight regarding the quality, safety and efficacy of the product under assessment.

Rwanda FDA reserves the right to request any additional information to establish the quality, safety and efficacy of medicines in Rwanda. During the assessment, additional data and/or samples may be requested through an official communication letter. Once a query has been issued to the applicant, the assessment process stops until Rwanda FDA receives a written response to the raised queries. Further processing of the application may only be undertaken if responses to queries issued in the official communication letter contains all outstanding information requested in one submission. Failure to comply with this condition or if the queries have been reissued for a **fourth** time and the applicant provides unsatisfactory responses, the application will be rejected.

In the event that the responses to the queries are not submitted within ninety (**90**) calendar days from the date they were issued, it will be considered that the applicant has withdrawn the application unless the applicant has requested for extension of deadline to Rwanda FDA. Thereafter, registration of the product may only be considered upon submission of a **new** application.

1.10. Compliance to the current Good Manufacturing Practices (cGMP)

The GMP inspection is part of the product registration process. Rwanda FDA should conduct inspection of the facility or use other means to verify whether the manufacturing site complies with cGMP regulations and/or guidelines before a product is registered. No product shall be registered unless the facility complies with cGMP. During the assessment, assessors may highlight GMPs issues and communicate to the department that has mandate of inspection and compliance. More information on GMP requirements and application for GMP inspection is detailed in the Rwanda FDA *Guidelines on Good Manufacturing Practices* and its annexes ***(Refer to the GMP guidelines document No DIS/GDL/002 and its annexes No DIS/GDL/003*)** downloadable from Rwanda FDA website.

1.11 Rwanda FDA Peer Review Committee for Product Registration

After Dossier Assessment Workshop (DAWO), a final dossier assessment report shall be presented to **Rwanda FDA Peer Review Committee (PRC)** before making final decisions for granting or rejecting registration of the product.

In the event, that there are safety, quality or efficacy issues to be resolved as per the decision of the PRC, the application shall remain pending until the resolution of the raised issues. If the applicant fails to provide the required data within ninety calendar days (**90**), the application shall be considered as **withdrawn.**

Rwanda FDA will register the product in the event that data on safety, quality and efficacy is considered satisfactory and a registration certificate of human medicinal products (***Refer to the Annex-X document n^{o}DHT/FMT/042)*** will be granted. The registration shall be valid for a period of five (**5**) years. In the event that the Rwanda FDA suspends or cancels the registration validity, a written official communication shall be made to the applicant.

1.11 Timelines for product registration

Product dossiers shall be scheduled for assessment according to the First in First out (FIFO) basis upon compliance of the requirements. A new application shall be processed within nine (**9**) months of receipt of the application. The applicant will be required to provide any requested additional data within ninety (**90)** calendar days. Additional data or query responses shall be processed within sixty (**60**) calendar days.

MODULE 1: ADMINISTRATIVE INFORMATION AND PRODUCT INFORMATION

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

1.1 Comprehensive table of contents for all modules

1.1.1 Cover letter

Applicants should include a cover letter with all applications. A copy of the letter should be placed at the beginning of Module 1. The cover letter for product registration shall be dated and signed by the applicant (***Refer to the Annex-I document N^{o} DHT/FMT/031***) downloadable from Rwanda FDA website in list of annexes to these guidelines.

1.1.2 Comprehensive table of contents

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

1.2 Application information

1.2.1 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. In case the product is being registered under trade name, a copy of trademark/proprietary name certificate issued by the relevant competent authority in Rwanda will be submitted. However, approved INN/generic name that are internationally recognised non-proprietary name of the product do not require the trademark/proprietary name certificate.

1.2.2. Application Form

An application to register a medicinal product for human use must be accompanied by a completed product application form ***(refer to the Annex II, document N^o DHT/FOM/031)*** downloadable from Rwanda FDA website. The application form should be duly filled with relevant information and attachments, dated signed and stamped appropriately.

1.3 Quality Information Summary (QIS)

The Quality Information Summary (QIS) template ***(refer to the Annex III, Document N^o DHT/FMT/033)*** be completed to provide a condensed summary of the key quality information for the PD and constitutes part of the submission package. The QIS provides an accurate record of technical data in the PD at the time of prequalification. The QIS is a condensed version of the QOS-PD in section 2.3 and represents the final agreed-upon key information on the API and FPP from the PD assessment (including, but not limited to, identification of the manufacturer(s), site addresses, API/FPP specifications, stability conclusions and relevant commitments).

1.4 Product Information

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

1.4.1 Prescribing information (Summary of Product Characteristics)

The prescribing information should be as described in the Rwanda FDA *Guidance on format and content of Summary of Product Characteristics for pharmaceutical products* ***(refer to document N^{o} DHT/GDL/010A****).*

1.4.2 Container labelling

The product should be labelled as prescribed in *Guidance on Format and Content of Labels for Pharmaceutical Products* (***Refer to document No-DHT/GDL/010B).***

1.4.3 Patient information leaflet (PIL)

All medicinal preparations with potential for long-term use and self-administered injections and Over the Counter (OTC) must contain a patient information leaflet as prescribed in the *Guidance on Format and Content of Patient Information Leaflets for Pharmaceutical Products* ***(Refer to document N^{o} DHT/GDL/010C)***

1.4.4 Mock-ups and specimens

The applicant should include mock-ups of the commercial sample.

1.4.5 Information about the experts

Experts must provide detailed reports of the documents and particulars, which constitute Modules 3, 4 and 5. The requirement for these signed Expert Reports may be met by providing

The Quality Overall Summary, Non-clinical Overview/Summary and Clinical Overview/ Summary in Module 2, A declaration signed by the experts in Module 1.
Brief information on the educational background, training and occupational experience of the experts.

Experts should additionally indicate in their declarations the extent, if any of their professional or other involvement with the applicant / dossier owner and confirm that the report has been prepared by them or if not, any assistance provided and by whom. Reports should be based on an independent assessment of the dossier and references must be provided for any additional claims not supported by the dossier. An Expert declaration form should be provided ***(refer to the Annex-IV, document N^{o} DHT/FOM/032)***

1.5 Certificates of Suitability to the CEP or APIMF

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

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

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

Complete copies of the CEP (including any annexes) should be provided in Module 1.7 Procedures relating to APIMFs and CEPs are outlined in more detail in Module 3.

The applicant should provide the Letter of Access to CEP or Letter of Access to APIMF, as appropriate from API manufacturer according to the formats for Letters of Access to CEP and APIMF ***(refer to the Annex V, document N^o DHT/FMT/034 and Annex VI, document N^o DHT/FMT/035)***. These letters should be included in Module 1.7.

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

1.6 Good Manufacturing Practice (GMP)

For all medicines, irrespective of the country of origin, all key manufacturing and/or processing steps in the production of active pharmaceutical ingredient, ingredients and finished pharmaceutical products must be performed in plants that comply with Rwanda FDA GMP guidelines. Attach a WHO-type certificate of GMP. More information on GMP requirements and application for GMP inspection is detailed in the Rwanda FDA *Guidelines on Good Manufacturing Practices* and its annexes ***(Refer to the GMP guidelines document N^o DIS/GDL/002 and its Annexes N^o DIS/GDL/003*)**.

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

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

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

1.8 Product registration status

1.8.1 Registration status within EAC and SRAs/WLAs

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

1.8.2 Statement on rejection or withdrawn application

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

1.9 Evidence of API and/or FPP prequalified by WHO

If an evidence indicating that the active pharmaceutical ingredient and/or finished pharmaceutical product are prequalified by WHO is available, it should be presented under this section.

1.10 Manufacturing and Marketing authorization

The applicant should submit a valid Certificate of Pharmaceutical Product in format recommended by the World Health Organization together with a valid Manufacturing Authorization for pharmaceutical production. In case the product has been WHO prequalified, the evidence should be submitted.

The applicant should submit proof of marketing authorization granted by other competent regulatory authorities if applicable.

1.11 Product samples

Two commercial samples in the final packing size with certificate of analysis and measuring devices where applicable should be submitted at the time of application for laboratory analysis and also to enable visual inspection of the product and product package. However, additional samples may be requested depending on tests or parameters to be carried out.

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

MODULE 2: OVERVIEW & SUMMARIES

2.1 Table of contents of Module 2

A table of contents for module 2 should be provided.

2.2 CTD Introduction

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

2.3 Quality overall summary (QOS)

The quality overall summary (QOS) is a summary that follows the scope and the outline of the Body of Data in Module 3. The QOS should not include information, data or justification that was not already included in Module 3 or in other parts of the CTD.

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

The quality overall summary – product dossiers (QOS-PD) template (***refer to the Annex VII, document N^{o} DHT/FMT/036)*** should be completed for generic pharmaceutical products containing APIs of synthetic or semi synthetic origin and their corresponding FPPs.

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

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

2.4. Non-Clinical overview

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

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

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

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

The Integrated Overview and Conclusions should clearly define the characteristics of the human pharmaceutical as demonstrated by the non-clinical 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 non-clinical findings for the safe human use of the pharmaceutical should be discussed (i.e., as applicable to labelling). *Refer to ICH Guidance on the Common Technical Document for the registration of pharmaceuticals for human use, Safety for guidance on the format and the content of this part.*

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

2.5. Clinical overview

The Clinical Overview is intended to provide a critical analysis of the clinical data in the Common Technical Document. The Clinical Overview will necessarily refer to application data provided in the comprehensive Clinical Summary, the individual clinical study reports (ICH E3), and other relevant reports; but it should primarily present the conclusions and implications of those data, and should not recapitulate them.

Specifically, the Clinical Summary should provide a detailed factual summarization of the clinical information in the CTD, and the Clinical Overview should provide a succinct discussion and interpretation of these findings together with any other relevant information. The clinical Overview should be presented in the following sequence

2.5.1 Product Development Rationale

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

a) Identify the pharmacological class of the FPP.

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

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

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

e) Note and explain concordance or lack of concordance with current standard research approaches regarding the design, conduct and analysis of the studies. Pertinent published literature should be referenced.

Regulatory guidance and advice (at least from the region(s) where the Clinical Overview is being submitted) should be identified, with discussion of how that advice was implemented. Formal advice documents (e.g., official meeting minutes, official guidance, letters from regulatory authorities) should be referenced, with copies included in the references section of Module 5.

2.5.2 Overview of Bio-pharmaceutics

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

2.5.3 Overview of Clinical Pharmacology

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

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

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

2.5.4 Overview of Efficacy

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

Prematurely terminated studies should be noted and their impact considered.

The following issues should generally be considered:

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

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

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

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

2.5.5 Overview of Safety

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

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

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

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

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

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

f) Common and non-serious adverse events, with reference to the tabular presentations of events with the test drug and with control agents in the Clinical Summary. The discussion

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

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

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

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

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

k) Long-term safety (E1a).

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

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

n) World-wide marketing experience. The extent of the world wide experience should be briefly discussed:

- any new or different safety issues identified.
- any regulatory actions related to safety.

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

2.5.6 Benefits and Risks Conclusions

The purpose of this section is to integrate all of the conclusions reached in the previous sections about the bio pharmaceutics, clinical pharmacology, efficacy and safety of the FPP and to provide an overall appraisal of the benefits and risks of its use in clinical practice. Also, implications of any deviations from regulatory advice or guidelines and any important limitations of the available data should be discussed here. This assessment should address critical aspects of the proposed Prescribing Information. This section should also consider the risks and benefits of the FPP as they compare to available alternative treatments or to no treatment in illnesses where no treatment may be a medically acceptable option; and should clarify the expected place of the FPP in the armamentarium of treatments for the proposed indication. If there are risks to individuals other than those who will receive the drug, these risks should be discussed (e.g., risks of emergence of drug-resistant bacterial strains with widespread use of an antibiotic for minor illnesses). The analyses provided in previous sections should not be reiterated here.

This section often can be quite abbreviated when no special concerns have arisen and the drug is a member of a familiar pharmacological class.

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

a) The efficacy of the FPP for each proposed indication.
b) Significant safety findings and any measures that may enhance safety.
c) Dose-response and dose-toxicity relationships; optimal dose ranges and dosage regimens.
d) Efficacy and safety in sub-populations, e.g., those defined by age, sex, ethnicity, organ function, disease severity, and genetic polymorphisms.
e) Data in children in different age groups, if applicable, and any plans for a development programme in children.

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

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

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

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

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

2.5.7 Literature References

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

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

2.6 Non-clinical Written and Tabulated Summaries

The following order is recommended:

2.6.1 Non-clinical Written Summaries

This guideline is intended to assist authors in the preparation of non-clinical 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 Non-Clinical Written Summary sections are described below. It should be emphasised that no guideline can cover all eventualities, and common sense and a clear focus on the needs of the regulatory authority assessor are the best guides to constructing an acceptable document. Therefore, applicants can modify the format if needed to provide the best possible presentation of the information, in order to facilitate the understanding and evaluation of the results. Whenever appropriate, age- and gender-related effects should be discussed. Relevant findings with stereoisomers and/or metabolites should be included, as appropriate. Consistent use of units throughout the Summaries will facilitate their review. A table for converting units might also be useful.

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

Order of Presentation of Information within Sections

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

Species should be ordered as follows:

a) Mouse
b) Rat

c) Hamster
d) Other rodent
e) Rabbit
f) Dog
g) Non-human primate
h) Other non-rodent mammal
i) Non-mammals

Routes of administration should be ordered as follows:

The intended route for human use:

a. Oral
b. Intravenous
c. Intramuscular
d. Intraperitoneal
e. Subcutaneous
f. Inhalation
g. Topical
h. Other

Use of Tables and Figures

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

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

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

Length of Nonclinical Written Summaries

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

Sequence of Written Summaries and Tabulated Summaries

The following order is recommended:

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

2.6.2. Content of Non-Clinical Written and Tabulated Summaries

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:

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

2.6.3 Pharmacology Written Summary

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

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

2.6.3.1 Brief Summary

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

2.6.3.2 Primary Pharmacodynamics

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

2.6.3.3 Secondary Pharmacodynamics

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

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

2.6.3.4 Safety Pharmacology

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

2.6.3.5 Pharmacodynamics Drug Interactions

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

2.6.3.6 Discussion and Conclusions

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

2.6.3.7 Tables and Figures

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

2.6.4. Pharmacokinetics Written Summary

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

a) Brief Summary
b) Methods of Analysis
c) Absorption
d) Distribution
e) Metabolism
f) Excretion
g) Pharmacokinetic Drug Interactions
h) Other Pharmacokinetic Studies
i) Discussion and Conclusions
j) Tables and Figures (either here or included in text)

2.6.4.1. Brief Summary

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

2.6.4.2 Methods of Analysis

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

2.6.4.3 Absorption

The following data should be summarised in this section:

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

2.6.4.4 Distribution

The following data should be summarised in this section:

a) Tissue distribution studies
b) Protein binding and distribution in blood cells
c) Placental transfer studies

2.6.4.5 Metabolism (interspecies comparison)

The following data should be summarised in this section:

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

2.6.4.6 Excretion

The following data should be summarised in this section:

a) Routes and extent of excretion
b) Excretion in milk

2.6.4.7 Pharmacokinetic Drug Interactions

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

2.6.4.8 Other Pharmacokinetic Studies

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

2.6.4.9. Discussion and Conclusions

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

2.6.4.10. Tables and Figures

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

2.6.5. Toxicology Written Summary

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

a) Brief Summary
b) Single-Dose Toxicity
c) Repeat-Dose Toxicity
d) Genotoxicity
e) Carcinogenicity
f) Reproductive and Developmental Toxicity
g) Studies in Juvenile Animals

h) Local Tolerance

i) Other Toxicity Studies

j) Discussion and Conclusions

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

2.6.5.1. Brief Summary

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

TOXICOLOGY PROGRAM 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 po	Rat and mouse	Metabolite x
Repeat-dose toxicity 1 month 6 months 9 months, etc.	po po po	Rat and dog Rat Rat	Paret drug

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

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

a) Fertility and early embryonic development

b) Embryo-foetal development

c) Prenatal and postnatal development, including maternal function

d) Studies in which the offspring (juvenile animals) are dosed and/or further evaluated, if such studies have been conducted. If modified study designs are used, the sub-headings should be modified accordingly.

2.6.5.2. Single-Dose Toxicity

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

2.6.5.3 Repeat-Dose Toxicity (including supportive toxicokinetics evaluation)

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

2.6.5.4 Genotoxicity

Studies should be briefly summarised in the following order:

a) in vitro non-mammalian cell system

b) in vitro mammalian cell system

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

d) Other systems

2.6.5.5 Carcinogenicity (including supportive toxicokinetics evaluations)

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

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

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

c) Other studies

2.6.5.6 Reproductive and Developmental Toxicity

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

a) Fertility and early embryonic development

b) Embryo-fetal development

c) Prenatal and postnatal development, including maternal function

d) Studies in which the offspring (juvenile animals) are dosed and/or further evaluated, if such studies have been conducted. If modified study designs are used, the sub-headings should be modified accordingly.

2.6.5.7 Local Tolerance

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

2.6.5.8 Other Toxicity Studies (if available)

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

a) Antigenicity (capacity if an antigen to bind to an antibody)
b) Immunotoxicity
c) Mechanistic studies (if not reported elsewhere)
d) Dependence
e) Studies on metabolites
f) Studies on impurities
g) Other studies

2.6.5.9 Discussion and Conclusions

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

2.6.5.10 Tables and Figures

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

2.6.6. Toxicology Tabulated Summary

Nonclinical Tabulated Summaries

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

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

The recommended formats for the tables in the Nonclinical Tabulated Summaries 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 Non-Clinical Written Summaries should be followed for the preparation of the tables for the Nonclinical Tabulated Summaries. *Refer to ICH Guidance on the Common Technical Document for the registration of pharmaceuticals for human use: Safety for guidance on the format and the content of this part.*

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

2.7. Clinical Summary

The Clinical Summary is intended to provide a detailed, factual summarization of all of the clinical information in the Common Technical Document. This includes information provided in ICH E3 clinical study reports; information obtained from any meta-analyses or other cross-study

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

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

The following order is recommended:

2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods

For generic products, Overview, summaries and conclusion should be filled in Bioequivalence Trial Information Summary (BITF) and ***(refer to* Annex VIII– *DHT/FMT/037)***.*

2.7.1.1 Background and Overview

This section should provide the reviewer with an overall view of the formulation development process, the *in vitro* and *in vivo* dosage form performance, and the general approach and rationale used in developing the bioavailability (BA), comparative BA, bioequivalence (BE), and *in vitro* dissolution profile database. Reference should be made to any guidelines or literature used in planning and conducting the studies. This section should also provide the reviewer with an overview of the analytical methods used, with emphasis on the performance characteristics of assay validation (e.g., linearity range, sensitivity, specificity) and quality control (e.g., accuracy and precision). This section should not include detailed information about individual studies.

2.7.1.2. Summary of Results of Individual Studies

A tabular listing of all biopharmaceutical studies should generally be provided, together with narrative descriptions of relevant features and outcomes of each of the individual studies that provided important *in vitro* or *in vivo* data and information relevant to BA and BE. The narrative descriptions should be brief, e.g., similar to an abstract for a journal article, and should describe critical design features and critical results. Similar studies may be described together, noting the individual study results and any important differences among the studies.

These narratives may be abstracted from the ICH E3 synopsis. References or electronic links to the full report of each study should be included in the narratives.

2.7.1.3 Comparison and Analyses of Results Across Studies

This section should provide a factual summary of all *in vitro* dissolution, BA, and comparative BA studies carried out with the drug substance or drug product, with particular attention to differences in results across studies. This overview should typically summarize 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, pharmacodynamics (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:

a) 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).

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

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

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

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

MODULE 3: QUALITY

3.1 Table of contents of Module 3

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

3.2 Body of data

3.2. S Active pharmaceutical ingredient (API)

The API information can be submitted to Rwanda FDA in one of the following four options:

a) Option 1: Full details in the Product Dossier (PD)

b) Option 2: Certificate of suitability of European Pharmacopeia (CEP)

c) Option 3: Active pharmaceutical ingredient pre-qualified by WHO or EAC approved APIMF

d) Option 4: Active Pharmaceutical Ingredient Master File (APIMF)

The applicant should clearly indicate at the beginning of the API section in the PD and in the QOS how the information on the API for each API manufacturer is being submitted.

Where reference is made to CEP, the finished product applicant must have written permission to access the CEP from the CEP holder. Applicant should provide the *Letter of Access to CEP*, as appropriate from API manufacturer (***Refer to the Annex V, Document N^{o} DHT/FMT/034*****).** Letter of access should be included in Module 1.5.

Where reference is made to APIMF, the finished product applicant must have written permission to access the APIMF from the company that supplied the APIMF and must provide the APIMF

file number to Rwanda FDA. Applicant should provide the *Letter of Access to APIMF*, as appropriate from API manufacturer (***Refer to the Annex VI, document N°DHT/FMT/036*).** Letter of access should be included in Module 1.5.

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

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

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

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

3.2.S.1 General information

3.2.S.1.1 Nomenclature

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

- (Recommended) International Non-proprietary 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), British Approved Name (BAN)); and

- Chemical Abstracts Service (CAS) registry number.

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

3.2.S.1.2 Structure

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

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

3.2. S.1.3 General properties

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

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

The physical and chemical properties of the API should be discussed including the physical description, solubilities in common solvents (e.g. water, alcohols, dichloromethane, acetone), quantitative aqueous pH solubility profile (e.g. pH 1.2 to 6.8, dose/solubility volume), polymorphism, pH and pKa values, UV absorption maxima and molar absorptivity, melting point, refractive index (for a liquid), hygroscopicity, partition coefficient, etc. (see table in the QOS). This list is not intended to be exhaustive, but provides an indication as to the type of information that could be included. Some of the more relevant properties to be considered for APIs are discussed below in greater detail.

Physical description

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

Solubilities/quantitative aqueous pH solubility profile

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

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

The solubilities over the physiological pH range (pH 1.2 to 6.8) in several buffered media should be provided in mg/ml. If this information is not readily available (e.g. literature references), it should be generated in-house.
For solid oral dosage forms, the dose/solubility volume should be provided as determined by:

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

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

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

For example, compound A has as its lowest solubility at 37 ± 0.5 °C, 1.0 mg/ml at pH 6.8 and is available in 100 mg, 200 mg and 400 mg strengths. This API would not be

considered a *BCS highly soluble* API as its dose/solubility volume is greater than 250 ml (400 mg/1.0 mg/ml = 400 ml).

Polymorphism

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

The description of manufacturing process and process controls (3.2.S.2.2) should indicate which polymorphic form is manufactured, where relevant; the literature references or studies performed to identify the potential polymorphic forms of the API, including the study results, should be provided in section 3.2.S.3.1; and if a polymorphic form is to be defined or limited (e.g. for APIs that are not *BCS highly soluble* and/or where polymorphism has been identified as an issue), details should be included in 3.2.S.4.1 through 3.2.S.4.5.

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

Particle size distribution

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

Information from literature

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

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

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

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

The list of manufacturers/companies should specify the *actual addresses* of production or manufacturing site(s) involved (including block(s) and units(s)), rather than the administrative offices. Telephone number(s), fax number(s) and e-mail address (es) should be provided.

A valid manufacturing authorization should be provided for the production of APIs. If available, a certificate of GMP compliance should be provided in the PD Module 1.

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

The description of the API manufacturing process represents the applicant's commitment for the manufacture of the API. Information should be provided to adequately describe the manufacturing process and process controls. For example, a flow diagram of the synthetic process (es) should be provided that includes molecular formulae, weights, yield ranges, chemical structures of starting materials, intermediates, reagents and API reflecting stereochemistry, and identifies operating conditions and solvents.

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

Alternate processes should be explained and described with the same level of detail as the primary process. Reprocessing steps should be identified and justified. Any data to support this justification should be either referenced or filed in 3.2.S.2.5.
The following requirements apply to the first option for submission of API information, where full details are provided in the dossier.

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

The recovery of materials, if any, should be described in detail with the step in which they are introduced into the process. Recovery operations should be adequately controlled such that impurity levels do not increase over time. For recovery of solvents, any processing to improve the quality of the recovered solvent should be described. Regarding recycling of filtrates

(mother liquors) to obtain second crops, information should be available on maximum holding times of mother liquors and maximum number of times the material can be recycled. Data on impurity levels should be provided to justify recycling of filtrates.

Where there are multiple manufacturing sites for one API manufacturer, a comprehensive list in tabular form should be provided comparing the processes at each site and highlighting any differences.

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

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

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

3.2.S.2.3 Control of materials

Materials used in the manufacture of the API (e.g. raw materials, starting materials, solvents, reagents, catalysts) should be listed, identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials meet standards appropriate for their intended use should be provided.

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

a) be a synthetic precursor of one or more synthesis steps prior to the final API intermediate. Acids, bases, salts, esters and similar derivatives of the API, as well as the racemate of a single enantiomer API, are not considered final intermediates;
b) be a well characterized, isolated and purified substance with its structure fully elucidated including its stereochemistry (when applicable);
c) have well-defined specifications that include among others one or more specific identity tests and tests and limits for assay and specified, unspecified and total impurities; and
d) be incorporated as a significant structural fragment into the structure of the API.

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

synthesis should be provided. A summary of the information on starting materials should be provided in the QOS- PD.

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

A letter of attestation should be provided confirming that the API and the starting materials and reagents used to manufacture the API are *without* risk of transmitting agents of animal spongiform encephalopathies.

3.2.S.2.4 Controls of critical steps and intermediates

Critical steps: Tests and acceptance criteria (with justification including experimental data) performed at critical steps identified in 3.2.S.2.2 of the manufacturing process to ensure that the process is controlled should be provided.

Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.
The critical steps should be identified. These can be among others: steps where significant impurities are removed or introduced, steps introducing an essential molecular structural element such as a chiral centre or resulting in a major chemical transformation, steps having an impact on solid-state properties and homogeneity of the API that may be relevant for use in solid dosage forms.

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

3.2. S.2.5 Process validation and/or evaluation

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

It is expected that the manufacturing processes for all APIs are properly controlled. If the API is prepared as sterile, a complete description should be provided for aseptic processing and/or sterilization methods. The controls used to maintain the sterility of the API during storage and transportation should also be provided. Alternate processes should be justified and described.

3.2.S.3 Characterization

3.2.S.3.1 Elucidation of structure and other characteristics

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

Elucidation of structure

The PD should include quality assurance (QA) certified copies of the spectra, peak assignments and a detailed interpretation of the data of the studies performed to elucidate and/or confirm the structure of the API. The QOS should include a list of the studies performed and a conclusion from the studies (e.g. if the results support the proposed structure).

For APIs that are not described in an officially recognized pharmacopoeia, the studies carried out to elucidate and/or confirm the chemical structure normally include elemental analysis, infrared (IR), ultraviolet (UV), nuclear magnetic resonance (NMR) and mass spectra (MS) studies. Other tests could include X-ray powder diffraction and differential scanning calorimetry (DSC).

For APIs that are described in an officially recognized pharmacopoeia, it is generally sufficient to provide copies of the IR spectrum of the API from each of the proposed manufacturer(s) run concomitantly with a pharmacopoeial reference standard.

Isomerism/Stereochemistry

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

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

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

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

Polymorphism

Many APIs can exist in different physical forms in the solid state. Polymorphism is characterized as the ability of an API to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice. Amorphous solids consist of disordered arrangements of molecules and do not possess a distinguishable crystal lattice. Solvates are crystal forms containing either stoichiometric or non-stoichiometric amounts of a solvent. If the incorporated solvent is water the solvates are also commonly known as hydrates.

Polymorphic forms of the same chemical compound differ in internal solid-state structure and, therefore, may possess different chemical and physical properties, including packing, thermodynamic, spectroscopic, kinetic, interfacial and mechanical properties. These properties can have a direct impact on API process ability, pharmaceutical product manufacturability and

product quality/performance, including stability, dissolution and bioavailability. Unexpected appearance or disappearance of a polymorphic form may lead to serious pharmaceutical consequences.

Applicants and API manufacturers are expected to have adequate knowledge about the polymorphism of the APIs used and/or produced. Information on polymorphism can come from the scientific literature, patents, compendia or other references to determine if polymorphism is a

concern, e.g. for APIs that are not *BCS highly soluble.* In the absence of published data for APIs that are not *BSC highly soluble*, polymorphic screening will be necessary to determine if the API can exist in more than one crystalline form.

Polymorphic screening is generally accomplished via crystallization studies using different solvents and conditions.

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

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

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

c) A description of the method used to prepare the solvate in 3.2.S.2.2.

Particle size distribution

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

3.2. S.3.2 Impurities

Information on impurities should be provided.

Details on the principles for the control of impurities (e.g. reporting, identification and qualification) are outlined in the ICH Q3A, Q3B and Q3C impurity guidelines. Discussion should be provided of the potential and actual impurities arising from the synthesis, manufacture or degradation of the API. This should cover starting materials, by-products, intermediates, chiral impurities and degradation products and should include the chemical names, structures and origins. The discussion of pharmacopoeial APIs should not be limited to the impurities specified in the API monograph. *(Refer to ICH Q3B: Impurities in New Drug Products, ICH Q3A: Impurities in New Drug Substances and ICH Q3C Impurities: Guideline for Residual Solvents)*

3.2. S.4 Control of the API

3.2. S.4.1 Specification

The specification for the API should be provided. Copies of the API specifications, dated and signed by authorized personnel (e.g. the person in charge of the quality control or quality assurance department) should be provided in the marketing authorization dossier, including specifications from each API manufacturer as well as those of the FPP manufacturer.

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

a) The *standard* declared by the applicant could be an officially recognized compendial standard (BP, JP, Ph.Eur, Ph.Int. and USP) or a house (manufacturer's) standard.

b) The *specification reference number and version (e.g. revision number and/or date*) should be provided for version control purposes.

c) For the analytical procedures, the *type* should indicate the kind of analytical procedure used (e.g. visual, IR, UV, HPLC, laser diffraction), the *source* refers to the origin of the analytical procedure (BP, JP, Ph.Eur, Ph.Int, USP, in-house) and the *version (e.g. code number/version/date)* should be provided for version control purposes.

In cases where there is more than one API manufacturer, the FPP manufacturer's API specifications should be one single compiled set of specifications that is identical for each manufacturer. It is acceptable to lay down in the specification more than one acceptance criterion and/or analytical method for a single parameter with the statement "for API from manufacturer A" (e.g. in the case of residual solvents).

Any non-routine testing should be clearly identified as such and justified along with the proposal on the frequency of non-routine testing.

3.2.S.4.2 Analytical procedures

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

3.2. S.4.3 Validation of analytical procedures

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

Copies of the validation reports for the analytical procedures used to generate testing results provided in the PD, as well as those proposed for routine testing of the API by the FPP manufacturer, should be provided.

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

The compendial methods as published are typically validated based on an API or an FPP originating from a specific manufacturer. Different sources of the same API or FPP can contain impurities and/or degradation products that were not considered during the development of the monograph. Therefore, the monograph and compendial method should be demonstrated suitable to control the impurity profile of the API from the intended source(s).

In general verification is not necessary for compendial API assay methods. However, specificity of a specific compendial assay method should be demonstrated if there are any potential impurities that are not specified in the compendial monograph. If an officially recognized compendial method is used to control API-related impurities that are not specified in the monograph, full validation of the method is expected with respect to those impurities.

If an officially recognized compendial standard is claimed and an in-house method is used in lieu of the compendial method (e.g. for assay or for specified impurities), equivalency of the in-house and compendial methods should be demonstrated. This could be accomplished by performing duplicate analyses of one sample by both methods and providing the results from the study. For

impurity methods, the sample analyzed should be the API spiked with impurities at concentrations equivalent to their specification limits.

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

3.2. S.4.4 Batch analyses

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

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

Copies of the certificates of analysis, both from the API manufacturer(s) and the FPP manufacturer, should be provided for the profiled batches and any company responsible for generating the test results should be identified. This data is used to evaluate consistency in API quality. The FPP manufacturer's test results should be summarized in the QOS.

For quantitative tests (e.g. individual and total impurity tests and assay tests), it should be ensured that actual *numerical results* are provided rather than vague statements such as "within limits" or "conforms".

A discussion and justification should be provided for any incomplete analyses (e.g. results not tested according to the proposed specification).

3.2. S.4.5 Justification of specification

Justification for the API specification should be provided.

A discussion should be provided on the inclusion of certain tests, evolution of tests, analytical procedures and acceptance criteria, differences from the officially recognized compendial

standard(s), etc. If the officially recognized compendial methods have been modified or replaced, a discussion should be included.

The justification for certain tests, analytical procedures and acceptance criteria may have been discussed in other sections of the PD (e.g. impurities, particle-size distribution) and does not need to be repeated here, although a cross-reference to their location should be provided.
Refer to ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug

Substances and New Drug Products: Chemical Substances, for more guidance

3.2. S.5 Reference standards or materials

Information on the reference standards or reference materials used for testing of the API should be provided. Information should be provided on the reference standard(s) used to generate data in the PD, as well as those to be used by the FPP manufacturer in routine API and FPP testing.

The source(s) of the reference standards or materials used in the testing of the API should be provided (e.g. those used for the identification, purity, assay tests). These could be classified as *primary* or *secondary* reference standards.

A suitable primary reference standard should be obtained from an officially recognized pharmacopoeial source (BP, JP, Ph.Eur, Ph.Int, USP) where one exists and the lot number should be provided. Primary reference standards from officially recognized pharmacopoeial sources do not need further structural elucidation.

Otherwise a primary standard may be a batch of the API that has been fully characterized (e.g. by IR, UV, NMR, MS analyses). Further purification techniques may be needed to render the material acceptable for use as a chemical reference standard. The purity requirements for a chemical reference substance depend upon its intended use. A chemical reference substance proposed for an identification test does not require meticulous purification, since the presence of a small percentage of impurities in the substance often has no noticeable effect on the test. On the

other hand, chemical reference substances that are to be used in assays should possess a high degree of purity (such as 99.5% on the dried or water-/solvent-free basis). Absolute content of the primary reference standard must be declared and should follow the scheme:

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

A secondary (or in-house) reference standard can be used by establishing it against a suitable primary reference standard, e.g. by providing legible copies of the IR of the primary and secondary reference standards run concomitantly and by providing its certificate of analysis, including assay determined against the primary reference standard. A secondary reference standard is often characterized and evaluated for its intended purpose with additional procedures other than those used in routine testing (e.g. if additional solvents are used during the additional purification process that are not used for routine purposes).

3.2. S.6 Container-closure system

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

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

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

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

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

3.2. S.7. Stability

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. The *Rwanda FDA Guidance on Stability Testing for Active Pharmaceutical Ingredients and Finished Pharmaceutical Products* ***(refer to document No DHT/GDL/001D)*** should be consulted for recommendations on the core stability data package required for product registration. Stress testing of the API can help identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. Photostability testing should be an integral part of stress testing. The standard conditions are described in ICH Q1B. If "protect from light" is stated in one of the officially recognized pharmacopoeia for the API, it is sufficient to state "protect from light" on labelling, in lieu of photostability studies, when the container closure system is shown to be light protective.

Accelerated and long-term stability testing

Available information on the stability of the API under accelerated and long-term conditions should be provided, including information in the public domain or obtained from scientific literature. The source of the information should be identified. The required long-term storage

conditions for APIs for the registration of the product is either 30ºC±2ºC/65%±5%RH or 30ºC±2ºC/75%±5%RH. Studies covering the proposed retest period at the above mentioned long-term storage conditions will provide better assurance of the stability.

b) Option 2: Certificate of suitability of European Pharmacopeia (CEP)

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

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

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

a) *3.2. S.1.3 General properties* – discussions on any additional applicable physicochemical and other relevant API properties that are not controlled by the CEP and EP monograph, e.g. solubilities and polymorphs as per guidance in this section.
b) *3.2. S.3.1 Elucidation of structure and other characteristics* – studies to identify polymorphs (exception: where the CEP specifies a polymorphic form) and particle size distribution, where applicable, as per guidance in this section.
c) *3.2.S.4.1 Specification* – the specifications of the FPP manufacturer including all tests and limits of the CEP and EP monograph and any additional tests and acceptance criteria that are not controlled in the CEP and Ph.Eur monograph, such as polymorphs and/or particle size distribution.
d) *3.2. S.4.2/3.2.S.4.3 Analytical procedures and validation* – for any tests in addition to those in the CEP and Ph.Eur monograph.

e) *3.2. S.4.4 Batch analysis* – results from two batches of at least pilot scale, demonstrating compliance with the FPP manufacturer's API specifications.
f) *3.2. S.5 Reference standards or materials* – information on the FPP manufacturer's reference standards.
g) *3.2. S.6 Container-closure system* – specifications including descriptions and identification of primary packaging components.
h) 3.2. S.7 Stability – exception: where the CEP specifies a re-test period that is the same as or of longer duration than the re-test period proposed by the applicant.

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

c) Option 3: Active pharmaceutical ingredient pre-qualified by WHO of EAC approved APIMF

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

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

a) 3.2. S.1.3 General properties – discussions on any additional applicable physicochemical and other relevant API properties that are not controlled by the API manufacturer's specifications, e.g. solubilities and polymorphs according to the guidance in this section.
b) 3.2. S.2 – if the sterility of the FPP is based upon the sterile manufacture of the API then data on the sterilization process together with full validation data should be provided.
c) 3.2. S.3.1 Elucidation of structure and other characteristics – studies to identify polymorphs and particle size distribution, where applicable, according to the guidance in this section.

d) 3.2.S.4.1 Specification – the specifications of the FPP manufacturer including all tests and limits of the API manufacturer's specifications and any additional tests and acceptance criteria that are not controlled by the API manufacturer's specifications such as polymorphs and/or particle size distribution.
e) 3.2. S.4.2/3.2.S.4.3 Analytical procedures and validation – any methods used by the FPP manufacturer in addition to those in the API manufacturer's specifications.
f) 3.2. S.4.4 Batch analysis – results from two batches of at least pilot scale, demonstrating compliance with the FPP manufacturer's API specifications.
g) 3.2. S.5 Reference standards or materials – information on the FPP manufacturer's reference standards.
h) 3.2.S.7 Stability – data to support the retest period if either the proposed retest period is longer or the proposed storage conditions are at a higher temperature or humidity to that of the prequalified API.

d) Option 4: Active Pharmaceutical Ingredient Master File (APIMF)

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

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

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

3.2. P Finished pharmaceutical product (FPP)

3.2. P.1 Description and Composition of the FPP

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

3.2. P.1.1. Description of the dosage form

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

- Composition, i.e., list of all components of the dosage form, and their amount on a per-unit basis (including overages, if any with justification) 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). For FPPs supplied with reconstitution diluent(s) that are not commercially available or have not been assessed and considered acceptable, information on the diluent(s)should be provided in a separate FPP portion ("3.2.P"), as appropriate.
- The container closure used for the FPP (and accompanying reconstitution diluent, if applicable) should be briefly described, with further details provided under 3.2.P.7 Container closure system.

3.2. P.1.2. Composition

This is a list of all components of the dosage form, and their amount on a per unit basis (including overages, if any), the function of the ingredients, and a reference to their quality standards [e.g. compendial monographs (BP, USP, JP, Ph.Eur etc.) or manufacturer's specifications (IH)].
The tables in the QOS template should be used to summarize the composition of the FPP and express the quantity of each component on a per unit basis (e.g. mg per tablet, mg per ml, mg per vial) and quantity per batch. The individual ingredient for mixtures prepared in-house (e.g. coatings) should be included in the tables, where applicable.

All ingredients used in the manufacturing process should be included, including those that may not be added to every batch (e.g. acid and alkali), those that may be removed during processing (e.g. solvents) and any others (e.g. nitrogen, silicon for stoppers). If the FPP is formulated using

an active moiety, then the composition for the active ingredient should be clearly indicated (e.g. "1 mg of active ingredient base = 1.075 mg active ingredient hydrochloride"). All overages should be clearly indicated (e.g. "contains 2% overage of the API to compensate for manufacturing losses").

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

The function of each component (e.g. diluent/filler, binder, disintegrant, lubricant, glidant, granulating solvent, coating agent, antimicrobial preservative) should be stated. If an excipient performs multiple functions, the predominant function should be indicated.

3.2. P.1.3. Description of accompanying reconstitution diluent(s)

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

3.2. P.1.4. Type of container and closure for the dosage form and/or reconstitution diluent

The container-closure used for the FPP (and accompanying reconstitution diluent, if applicable) should be briefly described, with further details provided under 3.2.P.7 Container-closure system, e.g. "The product is available in HDPE bottles with polypropylene caps (in sizes of 30, 60 and 90 tablets or capsules) and in PVC/aluminium foil unit dose blisters (in packages of 100s) (cards of 5 × 2, 10 cards per package)."

3.2. P.2. Pharmaceutical development

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

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

Pharmaceutical development information should include, at a minimum:

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

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

References:

ICH Q8 guidelines: Pharmaceutical Development
ICH Q9 guidelines: Quality Risk Management

3.2. P.2.1 Components of the FPP

3.2. P.2.1.1 Active pharmaceutical ingredient

The compatibility of the API with excipients listed in 3.2.P.1 should be discussed. Additionally, key physicochemical characteristics (e.g. water content, solubility, and particle size distribution, polymorphic or solid state form) of the API that can influence the performance of the FPP should be discussed. For fixed-dose combinations, the compatibility of APIs with each other should be discussed (*Refer to Rwanda FDA Guidelines for registration of fixed dose combination pharmaceutical products*).

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

3.2. P.2.1.2 Excipients

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

3.2. P.2.2 Finished pharmaceutical product

3.2. P.2.2.1 Formulation development

A brief summary describing the development of the FPP should be provided, taking into consideration the proposed route of administration and usage. The differences between the comparative bioavailability or Bio waiver formulations and the formulation (i.e. composition) described in 3.2.P.1 should be discussed. Results from comparative in vitro studies (e.g. dissolution) or comparative in vivo studies (e.g. bioequivalence) should be discussed when appropriate.

If the proposed FPP is a functionally scored tablet, a study should be undertaken to ensure the uniformity of dose in the tablet fragments. The data provided in the PD application should include a description of the test method, individual values, mean and relative standard deviation (RSD) of

the results. Uniformity testing (i.e. content uniformity or mass variation, depending on the requirement for the whole tablet) should be performed on each split portion from a minimum of 10 randomly selected whole tablets.

In vitro dissolution or drug release

A discussion should be included as to how the development of the formulation relates to development of the dissolution method(s) and the generation of the dissolution profile.

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

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

3.2. P.2.2.2 Overages

Any overages in the formulation(s) described in 3.2.P.1 should be justified. Justification of an overage to compensate for loss during manufacture should be provided, including the step(s) where the loss occurs, the reasons for the loss and batch analysis release data (assay results).

3.2. P.2.2.3 Physicochemical and biological properties

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

3.2. P.2.3. Manufacturing process development

The selection and optimization of the manufacturing process described in 3.2.P.3.3, in particular its critical aspects, should be explained. Where relevant, the method of sterilization should be explained and justified. Where relevant, justification for the selection of aseptic processing or other sterilization methods over terminal sterilization should be provided.

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

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

3.2. P.2.4. Container-closure system

The suitability of the container-closure system (described in 3.2.P.7) used for the storage, transportation (shipping) and use of the FPP should be discussed. This discussion should consider, e.g. choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching) safety of materials of construction and performance (such as reproducibility of the dose delivery from the device when presented as part of the FPP).

The suitability of the container-closure system used for the storage, transportation (shipping) and use of any intermediate/in-process products (e.g. premixes, bulk FPP) should also be discussed.
Refer to FDA Guidance for industry on container closure systems for Packaging Human Drugs and Biologics on https://www.fda.gov/media/70788/download

3.2. P.2.5. Microbiological attributes

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

Where an antimicrobial preservative is included in the formulation, the amount used should be justified by submission of results of the product formulated with different concentrations of the preservative(s) to demonstrate the least necessary but still effective concentration. The effectiveness of the agent should be justified and verified by appropriate studies (e.g. USP or Ph. Eur general chapters on antimicrobial preservatives) using a batch of the FPP. If the lower limit for the proposed acceptance criterion for the assay of the preservative is less than 90.0%, the effectiveness of the agent should be established with a batch of the FPP containing a concentration of the antimicrobial preservative corresponding to the lower proposed acceptance criteria.

3.2. P.2.6. Compatibility

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

Where a device is required for oral liquids or solids (e.g. solutions, emulsions, suspensions and powders/granules for such reconstitution) that are intended to be administered immediately after being added to the device, the compatibility studies mentioned in the following paragraphs are not required.

Where sterile, reconstituted products are to be further diluted, compatibility should be demonstrated with all diluents over the range of dilution proposed in the labelling. These studies should preferably be conducted on aged samples. Where the labelling does not specify the type of containers, compatibility (with respect to parameters such as appearance, pH, assay, levels of individual and total degradation products, sub-visible particulate matter and extractables from the packaging components) should be demonstrated in glass, PVC and polyolefin containers.

However, if one or more containers are identified in the labelling, compatibility of admixtures needs to be demonstrated only in the specified containers.

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

Refer ICH Q8 guidelines: Pharmaceutical Development for more guidance

Note: For an established non sterile generic product, a product quality review may satisfy the requirements of sections 3.2.P.2.2.1 (a), 3.2.P.2.3 (a) of the PD and QOS as stipulated in the *Guidance for Product Quality Review (PQR) requirements for generic medicinal products* ***(Refer to document N^{o} DHT/GDL/001E***)

3.2. P.3 Manufacture

3.2. P.3.1 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.

The facilities involved in the manufacturing, packaging, labelling and testing should be listed. If certain companies are responsible only for specific steps (e.g. manufacturing of an intermediate) it should be clearly indicated. The list of manufacturers/companies should specify the actual addresses of production or manufacturing site(s) involved (including block(s) and unit(s)), rather than the administrative offices.

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

3.2. P.3.2 Batch formula

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

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

All ingredients used in the manufacturing process should be included, including those that may not be added to every batch (e.g. acid and alkali), those that may be removed during processing (e.g. solvents) and any others (e.g. nitrogen, silicon for stoppers). If the FPP is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated (e.g. "1 kg of active ingredient base =1.075 kg active ingredient hydrochloride"). All overages should be clearly indicated (e.g. "Contains 5 kg (corresponding to 2%) overage of the API to compensate for manufacturing losses").

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

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

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

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

Steps in the process should have the appropriate process parameters identified, such as time, temperature or pH. Associated numeric values can be presented as an expected range. Numeric ranges for critical steps should be justified in section 3.2.P.3.4. In certain cases, environmental conditions (e.g. low humidity for an effervescent product) should be stated.

The maximum holding time for bulk FPP prior to final packaging should be stated. The holding time should be supported by the submission of stability data, if longer than 30 days. For an aseptic FPP, the holding time of the filtered product prior to filling should be supported by the submission of stability data, if longer than 24 hours.

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

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

3.2. P.3.4 Controls of critical steps and intermediates

Critical steps: tests and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps identified in 3.2.P.3.3 of the manufacturing process, to ensure that the process is controlled.

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

Examples of applicable in-process controls include:

(a) Granulations: moisture (limits expressed as a range), blend uniformity (e.g. low-dose tablets), bulk and tapped densities and particle size distribution;

(b) Solid oral products: average weight, weight variation, hardness, thickness, friability, and disintegration checked periodically throughout compression, weight gain during coating;

(c) Semi-solids: viscosity, homogeneity, pH;

(d) Transdermal dosage forms: assay of API–adhesive mixture, weight per area of coated patch without backing;

(e) Metered dose inhalers: fill weight or volume, leak testing, valve delivery;

(f) Dry powder inhalers: assay of API–excipient blend, moisture, weight variation of individually contained doses such as capsules or blisters;

(g) Liquids: pH, specific gravity, clarity of solutions;

(h) Parenterals: appearance, clarity, fill volume or weight, pH, filter integrity tests, particulate matter, leak testing of ampoules, pre-filtration and/or pre-sterilization bio-burden testing.

3.2. P.3.5 Process validation and/or evaluation

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

For product that meet the criteria of an established FPP, a product quality review as outlined in the *Guidance for Product Quality Review (PQR) requirements for generic medicinal products* ***(refer to document DHT/GDL/001E)*** may be submitted in lieu of the information below.

The following information should be provided:

a) A copy of the *process validation protocol*, specific to this FPP, that identifies the critical equipment and process parameters that can affect the quality of the FPP and defines testing parameters, sampling plans, analytical procedures and acceptance criteria;

b) A *commitment* that three consecutive, production-scale batches of this FPP will be subjected to *prospective validation* in accordance with the above protocol. The applicant should submit a written commitment that information from these studies will be available for verification) If the process validation studies have already been conducted (e.g. for sterile products), a copy of the process validation report should be provided in the PD in lieu of (a) and (b) above.

The process validation protocol should include inter alia the following:

a) a reference to the current master production document;
b) a discussion of the critical equipment;
c) the process parameters that can affect the quality of the FPP (critical process parameters (CPPs)) including challenge experiments and failure mode operation;
d) details of the sampling: sampling points, stages of sampling, methods of sampling and the sampling plans (including schematics of blender/storage bins for uniformity testing of the final blend);
e) the testing parameters/acceptance criteria including in-process and release specifications and including comparative dissolution profiles of validation batches against the batch(es) used in the bioavailability or Bio waiver studies;
f) the analytical procedures or a reference to appropriate section(s) of the dossier;
g) the methods for recording/evaluating results; and
h) the proposed timeframe for completion of the protocol.

The manufacture of sterile FPPs needs a well-controlled manufacturing area (e.g. a strictly controlled environment, highly reliable procedures and appropriate in-process controls). A detailed description of these conditions, procedures and controls should be provided.

The sterilization process should be described in detail and evidence should be provided to confirm that it will produce a sterile product with a high degree of reliability and that the physical and chemical properties as well as the safety of the FPP will not be affected. Details such as temperature range and peak dwell time for an FPP and the container-closure should be provided. Although standard autoclaving cycles of 121 °C for 15 minutes or more would not need a detailed rationale, such justifications should be provided for reduced temperature cycles or elevated temperature cycles with shortened exposure times. If ethylene oxide is used, studies and acceptance criteria should control the levels of residual ethylene oxide and related compounds.
Filters used should be validated with respect to pore size, compatibility with the product, absence of extractables and lack of adsorption of the API or any of the components.

For the validation of aseptic filling of parenteral products that cannot be terminally sterilized, simulation process trials should be conducted. This involves filling ampoules with culture media under normal conditions, followed by incubation and control of microbial growth. Results on microbial contamination levels should be provided.

Note: For an established generic product a product quality review may satisfy the requirements of sections 3.2.P.2.2.1 (a), 3.2.P.2.3 (a) and 3.2.P.3.5 of the PD and QOS ***(refer to the Annex VII, document N^{o} DHT/FMT/036)***

3.2. P.4 Control of excipients

3.2. P.4.1 Specifications

The specifications for excipients should be provided.

The specifications from the FPP manufacturer should be provided for all excipients, including those that may not be added to every batch (e.g. acid and alkali), those that do not appear in the final FPP (e.g. solvents) and any others used in the manufacturing process (e.g. nitrogen, silicon for stoppers).

If the standard claimed for an excipient is an officially recognized compendial standard, it is sufficient to state that the excipient is tested according to the requirements of that standard, rather than reproducing the specifications found in the officially recognized compendial monograph.
If the standard claimed for an excipient is a non-compendial standard (e.g. house standard) or includes tests that are supplementary to those appearing in the officially recognized compendial monograph, a copy of the specification for the excipient should be provided.

For excipients of natural origin, microbial limit testing should be included in the specifications.

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

The colours permitted for use are limited to those listed in the "Japanese pharmaceutical excipients", the EU "List of permitted food colours", and the FDA "Inactive ingredient guide". For proprietary mixtures, the supplier's product sheet with the qualitative formulation should be submitted, in addition to the FPP manufacturer's specifications for the product including identification testing.

For flavours the qualitative composition should be submitted, as well as a declaration that the excipients comply with foodstuff regulations (e.g. USA or EU).

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

3.2. P.4.2 Analytical procedures

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

3.2. P.4.3 Validation of analytical procedures

Analytical validation information, including experimental data, for the analytical procedures used for testing the excipients should be provided as in accordance to ICHQ6.

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

3.2. P.4.4 Justification of specifications

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

A discussion of the tests that are supplementary to those appearing in the officially recognized compendial monograph should be provided. *Refer to ICH Q2 and ICH Q6A for more guidance.*

3.2. P.4.5 Excipients of human or animal origin

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

The following excipients should be addressed in this section: gelatin, phosphates, stearic acid, magnesium stearate and other stearates. If from plant origin a declaration to this effect will suffice.

For these excipients from animal origin, a letter of attestation should be provided confirming that the excipients used to manufacture the FPP are *without* risk of transmitting agents of animal spongiform encephalopathies.

Reference:

a) *ICH Q5A Viral Safety Evaluation of Biotechnology Products derived from Cell Lines of Human or Animal Origin.*
b) *ICH Q5D Quality of Biotechnological Products: Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products.*
c) *ICH Q6B Test Procedures and Acceptance Criteria for Biotechnological/Biological Products.*

3.2. P.4.6 Novel excipients

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

3.2. P.5 Control of FPP

3.2. P.5.1 Specification(s)

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

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

Skip testing is acceptable for parameters such as identification of colouring materials and microbial limits, when justified by the submission of acceptable supportive results for five

production batches. When skip-testing justification has been accepted, the specifications should include a footnote, stating at minimum the following skip-testing requirements: at minimum every tenth batch and at least one batch annually is tested. In addition, for stability- indicating parameters such as microbial limits, testing will be performed at release and shelf- life during stability studies.

Refer to ICH Q3B, Q3C, Q6A for more guidance.

3.2. P.5.2 Analytical procedures

The analytical procedures used for testing the FPP should be provided. Copies of the in-house analytical procedures used during pharmaceutical development (if used to generate testing results provided in the PD) as well as those proposed for routine testing should be provided. Unless modified, it is not necessary to provide copies of officially recognized compendial analytical procedures. *Refer to ICH Q2 for more guidance.*

3.2. P.5.3 Validation of analytical procedures

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

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

As recognized by regulatory authorities and pharmacopoeias themselves, verification of compendial methods can be necessary. The compendial methods, as published, are typically validated based on an API or an FPP originating from a specific manufacturer. Different sources of the same API or FPP can contain impurities and/or degradation products or excipients that were not considered during the development of the monograph. Therefore, the monograph and compendial method(s) should be demonstrated suitable for the control of the proposed FPP.

For officially recognized compendial FPP assay methods, verification should include a demonstration of specificity, accuracy and repeatability (method precision). If an officially recognized compendial method is used to control related substances that are not specified in the monograph, full validation of the method is expected with respect to those related substances.

If an officially recognized compendial standard is claimed and an in-house method is used in lieu of the compendial method (e.g. for assay or for related compounds), equivalency of the in-house and compendial methods should be demonstrated. This could be accomplished by performing duplicate analyses of one sample by both methods and providing the results from the study. For related compound methods, the sample analysed should be the placebo spiked with related compounds at concentrations equivalent to their specification limits. *Refer to ICH Q2 for guidance*

3.2. P.5.4 Batch analyses

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

Information should include strength and batch number, batch size, date and site of production and use (e.g. used in comparative bioavailability or Bio waiver studies, preclinical and clinical studies (if relevant), stability, pilot, scale-up and if available, production-scale batches) on relevant FPP batches used to establish the specification(s) and evaluate consistency in manufacturing.
Analytical results tested by the company responsible for the batch release of the FPP should be provided for not less than two batches of at least one commercial scale batch and two pilot scale batches.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as “all tests meet specifications”. This should include ranges of analytical results where relevant. For quantitative tests (e.g. individual and total impurity tests and assay tests), it should be ensured that actual *numerical results* are provided rather than vague statements such as “within limits” or “conforms” (e.g. “levels of degradation product A ranged

from 0.2 to 0.4%"). Dissolution results should be expressed at minimum as both the average and range of individual results. Copies of signed and dated certificate of analysis of at least two (2) batches should be provided in PD.

A discussion and justification should be provided for any incomplete analyses (e.g. results not tested according to the proposed specification). *Refer to ICH Q3B, Q3C and Q6A for more guidance.*

3.2. P.5.5 Characterization of impurities

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

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

3.2. P.5.6 Justification of specification(s)

Justification for the proposed FPP specification(s) should be provided. A discussion should be provided on the omission or inclusion of certain tests, evolution of tests, analytical procedures and acceptance criteria, differences from the officially recognized compendial standard(s), etc. If the officially recognized compendial methods have been modified or replaced, a discussion should be included.

The justification for certain tests, analytical procedures and acceptance criteria (e.g. degradation products, dissolution method development) may have been discussed in other sections of the PD and does not need to be repeated here, although a cross-reference to their location should be provided.

3.2.P.6 Reference standards or materials

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

See Section 3.2.S.5 for information that should be provided on reference standards or materials. Information should be provided on reference materials of FPP degradation products, where not included in 3.2.S.5.

3.2.P.7. Container-closure system

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

For non-functional secondary packaging components (e.g. those that neither provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information should be provided. Suitability information should be located in 3.2.P.2.
The officially recognized pharmacopeia should be consulted for recommendation on the packaging information for FPPs.

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

a) in direct contact with the dosage form (e.g. container, closure, liner, desiccant, filler);
b) used for drug delivery (including the device(s) for multi-dose solutions, emulsions, suspensions and powders/granules for such);
c) used as a protective barrier to help ensure stability or sterility; and

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

The Specifications for the primary packaging components should include a specific test for identification (e.g. IR). Specifications for film and foil materials should include limits for thickness or area weight. The pack size for HDPE containers shall not exceed **90 tablets or capsules.** *Refer to FDA Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics* for more guidance.

3.2.P.8. Stability

The purpose of stability testing is to provide evidence of how the quality of an API or FPP varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The stability programme also includes the study of product-related factors that influence its quality, for example, interaction of API with excipients, container-closure systems and packaging materials. Detailed information available in the *Guidance on Stability Testing for Active Pharmaceutical Ingredients and Finished Pharmaceutical Products* (***Refer to document N^{o} DHT/GDL/001D)***

3.2.P.8.1 Stability Summary and Conclusion

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

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

3.2.P.8.3 Stability Data

Results of the stability studies should be presented in an appropriate format (e.g. tabular, graphical and narrative). A summary of the studies undertaken (conditions, batches, analytical procedures)

and a brief discussion of the results and conclusions of the stability studies and analysis of data should be included. Conclusions with respect to storage conditions and shelf-life and, if applicable, in use storage conditions and shelf-life should be given. Stability studies should be provided for each pack type applied for registration. A tabulated summary of the stability results from 3.2.P.8.3, with graphical representation where appropriate, should be included. The post-approval stability protocol, as described in 3.2.P.8.2, should be provided. Information on the analytical procedures used to generate the data and validation of these procedures should be included according the *Rwanda FDA Guidance on stability testing for API and FPP* (***Refer to document N^{o} DHT/GDL/010D***).

3.2. REGIONAL INFORMATION

3.2. R.1. PRODUCTION DOCUMENTATION

3.2.R.1.1. Executed production documents

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

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

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

If not included in the executed batch records through sufficient in-process testing, data should be provided for the batch used in comparative bioavailability or Bio waiver studies that demonstrate

the uniformity of this batch. The data to establish the uniformity of the bio batch should involve testing to an extent greater than that required in routine quality control.

English translations of executed records should be provided where relevant.

3.2.R.1.2 Master production documents

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

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

a) master formula;
b) dispensing, processing and packaging sections with relevant material and operational details;
c) relevant calculations (e.g. if the amount of API is adjusted based on the assay results or on the anhydrous basis
d) Identification of all equipment by, at a minimum, type and working capacity (including make, model and equipment number, where possible);
e) process parameters (e.g. mixing time, mixing speed, milling screen size, processing temperature range, granulation end-point and tablet machine speed (expressed as target and range));
f) list of in-process tests (e.g. appearance, pH, assay, blend uniformity, viscosity, particle size distribution, loss on drying, weight variation, hardness, disintegration time, weight gain during coating, leaker test, minimum fill, clarity and filter integrity checks) and specifications;
g) sampling plan with regard to the:
    i. steps at which sampling should be done (e.g. drying, lubrication and compression),

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

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

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

i) for sterile products, reference to standard operating procedures

j) (SOPs) in appropriate sections and a list of all relevant SOPs at the end of the document;

k) theoretical and actual yield;

l) compliance with the GMP requirements.

3.2.R.2. ANALYTICAL PROCEDURES AND VALIDATION INFORMATION

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

3.3. LITERATURE REFERENCES

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

MODULE 4: NON CLINICAL STUDY REPORTS

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

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

This chapter presents an agreed format for the organization of the nonclinical reports in the Common Technical Document for applications that will be submitted to Rwanda FDA.

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

4.1 Table of Contents of Module 4

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

4.2 Study Reports

The study reports should be presented in the following order:

4.2.1 Pharmacology

Refer to ICH Guideline on Non clinical Safety Studies for the Conduct of Human Clinical Trials and marketing authorization for Pharmaceuticals (M3) for the non-clinical safety studies

recommended to support human clinical trials of a given scope and duration as well as marketing authorization for pharmaceuticals.

Refer to ICH Guideline on Safety Pharmacology Studies for Human Pharmaceuticals (S7A) for the definition, objectives and scope of safety pharmacology studies. It also addresses which studies are needed before initiation of Phase 1 clinical studies as well as information needed for marketing.

Refer to ICH Guideline on The Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarisation (QT Interval Prolongation) by Human Pharmaceuticals (S7B) for a non-clinical testing strategy for assessing the potential of a test substance to delay ventricular repolarisation. This Guideline includes information concerning non-clinical assays and integrated risk assessments.

4.2.1.1 Primary Pharmacodynamics

4.2.1.2 Secondary Pharmacodynamics

4.2.1.3 Safety Pharmacology

4.2.1.4 Pharmacodynamics Drug Interactions

4.2.2 Pharmacokinetics

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

4.2.2.2 Absorption

4.2.2.3 Distribution

4.2.2.4 Metabolism

4 2.2.5 Excretion

4.2.2.6 Pharmacokinetic Drug Interactions (nonclinical)

4.2.2.7 Other Pharmacokinetic Studies

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

4.2.3 Toxicology

Refer to ICH Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies (S3A) for guidance on developing test strategies in toxicokinetics and the need to integrate pharmacokinetics into toxicity testing, in order to aid in the interpretation of the toxicology findings and promote rational study design development.

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

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

Refer to The Committee for Human Medicinal Products (CHMP) Guideline on repeated dose toxicity for guidance on the conduct of repeated dose toxicity studies of active substances intended for human use.

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

4.2.3.3 Genotoxicity

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

Refer to the committee for medicinal products for human use (CHMP) guideline on the limits of genotoxic impurities for a general framework and practical approaches on how to deal with genotoxic impurities in new active substances. It also relates to new applications for existing active substances, where assessment of the route of synthesis, process control and impurity profile does not provide reasonable assurance that no new or higher levels of genotoxic impurities are introduced as compared to products currently authorized in the EU containing the same active substance. The same also applies to variations to existing Marketing Authorizations pertaining to the synthesis.

4.2.3.3.1 In vitro

4.2.3.3.2 In vivo (including supportive toxicokinetics evaluations)

4.2.3.4 Carcinogenicity (including supportive toxicokinetics evaluations)

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

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

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

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

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

4.2.3.4.3 Other studies

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

Refer to ICH Guidance on Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility (S5) for guidance on tests for reproductive toxicity. It defines the periods of treatment to be used in animals to better reflect human exposure to medical products and allow more specific identification of stages at risk.

Refer to the Committee for Medicinal Products for human use (CHMP) EMA-guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications for guidance on the need for, role and timing of studies in juvenile animals in the non-clinical safety evaluation of medicinal products for paediatric use.

4.2.3.5.1 Fertility and early embryonic development

4.2.3.5.2 Embryo-foetal development

4.2.3.5.3 Prenatal and postnatal development, including maternal function

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

4.2.3.6 Local Tolerance

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

4.2.3.7 Other Toxicity Studies (if available)

4.2.3.7.1 Antigenicity

4.2.3.7.2 Immunotoxicity

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

4.2.3.7.3 Mechanistic studies (if not included elsewhere)

4.2.3.7.4 Dependence

4.2.3.7.5 Metabolites

4.2.3.7.6 Impurities

4.2.3.7.7 Other toxicity studies

4.2.3.7.7.1 Photosafety evaluation

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

For specific products

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

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

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

MODULE 5: CLINICAL STUDY REPORTS

5.1 Table of Contents of Module 5

A table of contents for study reports should be provided.

5.2 Tabular Listing of all Clinical Studies

5.3 Clinical Study Reports

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

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

5.3.1 Reports of Biopharmaceutical Studies

5.3.1.1 Bioavailability (BA) Study Reports

5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports

Refer to the Rwanda FDA Guidance on therapeutic equivalence requirements ***(Refer to document No DHT/GDL/001F)*** *and Rwanda FDA Guidance for application of biopharmaceutical classification system Bio waiver (****Refer to document No DHT/GDL/001G)****.* In case that Bio waiver is applicable, the applicant must complete the *Bio waiver Application Form* ***(Refer to the Annex IX, document N^{o} DHT/FOM/033).***

5.3.1.3 *In vitro-In vivo* Correlation Study Reports

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

For Generic product

*Refer to the Rwanda FDA Guidance on Therapeutic Equivalence Requirements (**Refer to document No DHT/GDL/001F)*.

5.3.2 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials

5.3.2.1 Plasma Protein Binding Study Reports

5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies

5.3.2.3 Reports of Studies Using Other Human Biomaterials

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.1 Healthy Subject PK and Initial Tolerability Study Report

5.3.3.2 Patient PK and Initial Tolerability Study Reports

5.3.3.3 Intrinsic Factor PK Study Reports

5.3.3.4 Extrinsic Factor PK Study Reports

5.3.3.5 Population PK Study Reports

5.3.4. Reports of Human Pharmacodynamics (PD) Studies

5.3.4.1 Healthy Subject PD and PK/PD Study Reports

5.3.4.2 Patient PD and PK/PD Study Reports

5.3.5. Reports of Efficacy and Safety Studies

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

5.3.5.2 Study Reports of Uncontrolled Clinical Studies

5.3.5.3 Reports of Analyses of Data from More Than One Study

5.3.5.4 Other Clinical Study Reports

5.3.6 Reports of Post-Marketing Experience if available

5.3.7 Case Report Forms and Individual Patient Listings

Refer to Rwanda FDA Guidance on Therapeutic Equivalence Requirements ***(Refer to document No DHT/GDL/001F)***

5.4 Literature References

Refer to the list of the ICH guidelines on clinical studies

Commission regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food.

- Committee for Medicinal Products for Human Use (CHMP). *Guideline on the limits of genotoxic impurities*. European Medicines Agency, 2006 (CPMP/SWP/5199/02 EMEA/ CHMP/QWP/251344/2006).
- Committee for Medicinal Products for Human Use (CHMP). Guideline on the specification limits for residues of metal catalysts or metal reagents. London, European Medicines Agency, 2008 (EMEA/CHMP/SWP/4446/2000).
- *Committee on Specifications for Pharmaceutical Preparations. Forty-second report.* Geneva, World Health Organization, 2008, Annex 4 (WHO Technical Report Series, No. 948).
- *Common technical document for the registration of pharmaceuticals for human use – quality questions & answers/location issues.*
    - European Medicines Agency, 2009
    - (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/ WC500002726.pdf).
- Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2003.

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- Containers – glass. In: *United States Pharmacopeia*, 2nd suppl. Rockville, MD, 2007.
- Containers – plastic. In: *United States Pharmacopeia*, 2nd suppl. Rockville, MD, 2007.
- Elastomeric closures for injections, In: *United States Pharmacopeia*, 2nd suppl. Rockville,
    - MD, 2007: 144–145.
- *Excipients in the label and package leaflet of medicinal products for human use*. 2003(CPMP/463/00)http://www.ema.europa.eu/docs/en_GB/document_library/ Scientific guideline/2009/09/WC500003412.pdf.
- General guidelines for the establishment, maintenance and distribution of chemical reference substances. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first report.* Geneva, World Health Organization, 2007, Annex 3 (WHO Technical Report Series, No. 943).
- Glass containers for pharmaceutical use. In: *European Pharmacopoeia*. Strasbourg,
    - European Directorate for the Quality of Medicines, 2010: 303–307.
- Good manufacturing practices for pharmaceutical products: main principles. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report.* Geneva, World Health Organization, 2011, Annex 3 (WHO Technical Report Series, No. 961).
- Guidelines for registration of fixed-dose combination medicinal products. Appendix 3: Pharmaceutical development (or pre formulation) studies. Table A1: Typical stress conditions in pre formulation stability studies. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth report.* Geneva, World Health Organization, 2005, Annex 5 (WHO, Technical Report Series, No. 929).
- Guidelines on active pharmaceutical ingredient master file procedure. In: *WHO Expert*
- Guidelines on packaging for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report.* Geneva, World Health Organization, 2002, Annex 9 (WHO Technical Report Series, No. 902).
- Guidelines on submission of documentation for a multisource (generic) finished product: general format: preparation of product dossiers in common technical document format.

In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth report.* Geneva, World Health Organisation, 2011, Annex 5 (WHO Technical Report Series, No. 961).

- *ICH harmonized tripartite guideline impurities: guideline for residual solvents – Q3C*.
- *ICH harmonized tripartite guideline: bracketing and matrixing designs for stability testing of new drug substances and products – Q1D*. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2002.
- *ICH Harmonised tripartite guideline: derivation and characterisation of cell substrates used for production of biotechnological/biological products – Q5D*. Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1997.
- *ICH Harmonized tripartite guideline: evaluation for stability data – Q1E*. International
- *ICH Harmonized tripartite guideline: Good manufacturing practice guide for active pharmaceutical ingredients – Q7*. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2000
- *ICH Harmonized tripartite guideline: impurities in new drug products – Q3B.* International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2006.
- *ICH Harmonized tripartite guideline: impurities in new drug substances – Q3A. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2006.*
- *ICH Harmonized tripartite guideline: pharmaceutical development – Q8*. International
- *ICH Harmonized tripartite guideline: pharmaceutical quality system – Q10*. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2008.
- *ICH Harmonized tripartite guideline: quality risk management – Q9*. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2005.
- *ICH Harmonized tripartite guidelines: specifications: test procedures and acceptance*

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- *ICH Harmonized tripartite guideline: specifications: test procedures and acceptance criteria for biotechnological/biological products – Q6B*. Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1999.
- *ICH Harmonized tripartite guideline: stability testing for new dosage forms: Annex to the ICH harmonized tripartite guideline on stability testing for new drugs and products – Q1C*. Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1996.
- *ICH Harmonized tripartite guideline: stability testing of new drug substances and products – Q1A*. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2003.
- ICH Harmonized tripartite guideline: *Stability testing: Photostability testing of new drug substances and products – Q1B*. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1996.
- *ICH Harmonized tripartite guideline: the common technical document for the registration*

  of pharmaceuticals for human use: quality – M4Q. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2002.
- *ICH Harmonized tripartite guideline: validation of analytical procedures: text and methodology – Q2*. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1994.
- *ICH Harmonized tripartite guideline: viral safety evaluation of biotechnology products derived from cell lines of human or animal origin – Q5A*. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2009.
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- Rowe RC, Sheskey PJ, Quinn ME, eds. *Handbook of pharmaceutical excipients,* 6th ed. London, Pharmaceutical Press, 2009.
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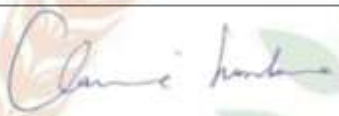
- Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-third report*. Geneva, World Health Organization, 2009, Annex 2 (WHO Technical Report Series, No. 953).
- US FDA Guidance for industry: Genotoxic and carcinogenic impurities in drug substances

  and products: recommended approaches. US Food and Drug Administration, 2008.
- WHO good distribution practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth report.* Geneva, World Health Organization, 2010, Annex 5 (WHO Technical Report Series, No. 957).
- WHO good manufacturing practices for active pharmaceutical ingredients. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth report.* Geneva, World Health Organization, 2010, Annex 2 (WHO Technical Report Series, No. 957).

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

ENDORSEMENT OF THE GUIDELINES

	Author	Authorized by	Approved by
Title	Division Manager of Drugs and Health Technologies	Head of Food and Drugs Assessment and Registration	Director General
Names	**Irasabwa Clarisse**	**Kabatende Joseph**	**Dr Karangwa Charles**
Signature			
Date	**20/4/2020**	**20/4/2020**	**20/4/2020**

ANNEXES

< Applicant>
< Address>
<Postal Code>
< Town>
<Country>
<Date>

<Rwanda FDA>
<P.O.BOX 84> <Kigali>
< Rwanda >

Dear Sir/Madam,

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

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

Name of the medicinal product(s): ……

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

INN/active Pharmaceutical ingredient(s): ……

ATC Code(s): ……

You will find enclosed the submission dossier as specified hereafter:

☐ CTD format, 2 soft copies documents format

☐ The relevant fees for this application have been paid.

☐ CD rom/external driver that contains summaries in word format and body data in PDF format

☐ We confirm that all future submissions for this specific product will be submitted in this same format

☐ We confirm that the electronic submission has been checked with up-to-date and state-of-the-art antivirus software.

☐ The electronic submission contains the following modules:

Module 1: Administrative information and product information

Module 2: Overview and summaries

Module 3: Quality

Module 4: Non clinical study reports

Module 5: Clinical study reports

☐ Type of Submission: ☐Full Application ☐Abridged Application

☐ I confirm that the Product Dossier information submitted including composition, formulation, strength, specifications and packaging is the same in all aspects as the product registered with the relevant SRA, WHO PQ and EAC (Only for Abridged Application)

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

Yours sincerely,

<Signature>

<Name>

<Title>

<Phone number(s)>

<Email address>

ANNEX II: PRODUCT REGISTRATION APPLICATION FORM

Application Number:	Rwanda FDA use only
Date of submission of the dossier	Rwanda FDA use only

MODULE 1: ADMINISTRATIVE INFORMATION	
1.0 PARTICULARS OF THE PRODUCT	
1.1	Type of the human medicine application New Generic Extension application Duplicate license Renewal* * If variation has been made, information supporting the changes should be submitted. See Rwanda FDA variation guidelines for registered medicinal products.
1.2	Proprietary Name
1.3	International Non-proprietary Name (INN) of the Active Pharmaceutical Ingredient (API)
1.4	Strength of Active Pharmaceutical Ingredient (API) per unit dosage form:
1.5	Name and address (physical and postal) of Applicant
(Company) Name: Address: Country: Telephone: Telefax: E-Mail:	
1.6	Name and address (physical and postal) of Local Technical Representative
(Company) Name: Address: Country: Telephone: Telefax: E-Mail:	
1.7	Pharmaceutical Dosage form* and route of administration* * List of standard terms for dosage forms and routes of administration is available in the Rwanda FDA the guidelines on submission of documentation for registration of human medicines
1.7.1	Dosage form:

ANNEX II: PRODUCT REGISTRATION APPLICATION FORM

1.7.2	Route(s) of administration (use current list of standard terms)
1.8	Packing/pack size:
1.9	Visual description (Add as many rows as necessary)
1.10	Proposed shelf life (in months):
1.10.1	Proposed shelf life (after reconstitution or dilution):
1.10.2	Proposed shelf life (after first opening container):
1.10.3	Proposed storage conditions:
1.10.4	Proposed storage conditions after first opening:
1.11	Other sister medicinal products registered or applied for registration
1.11.1	Do you hold Marketing Authorization (s) of other human medicine (s) containing the same active substance (s) in the Rwanda FDA? If yes state; ▪ Product name (s), strength (s), pharmaceutical form (s): ▪ Partner States where product is authorized: ▪ Marketing authorization number(s): ▪ Indication(s):
1.11.2	Have you applied for Marketing Authorization of human medicine (s) containing the same active substance (s) in the Rwanda FDA? ▪ Product name (s), strength (s), pharmaceutical form (s): ▪ Indication(s):
1.12	Pharmacotherapeutic group and ATC Code
1.12.1	Pharmacotherapeutic group:
1.12.2	ATC Code: (Please use current ATC code)
1.12.3	If no ATC code has been assigned, please indicate if an application for ATC code has been made: ☐
1.13	Distribution category: Controlled Drug ☐ POM ☐ Pharmacy Only ☐ OTC ☐ General sale ☐ (Applicants are invited to indicate which categories they are requesting, however, Rwanda FDA reserve the right to change and/or apply only those categories provided for in their national legislation)
1.14	Country of origin:
1.15	Product Marketing Authorization in the country of origin (Attach Certificate of Pharmaceutical Product from National Medicines Regulatory Authority). If not registered, state reasons

☐ Authorized Country: Date of authorization (dd-mm-yyyy): Proprietary name:	☐ Withdrawn (by applicant after authorization) Country: Date of withdrawal (dd-mm-yyyy): Proprietary name:

ANNEX II: PRODUCT REGISTRATION APPLICATION FORM

Authorization number: ☐ Refused Country: Date of refusal (dd-mm-yyyy): Reason for Refusal:	Reason for withdrawal: ☐ Suspended/revoked (by competent authority) Country: date of suspension/revocation (dd-mm-yyyy): Reason for suspension/revocation: Proprietary name:
1.16	List ICH and Observers where the product is approved.
1.17	Name(s) and complete physical address(es) of the manufacturer(s)
1.17.1	Name(s) and physical address (es) of the manufacturing site of the finished pharmaceutical product (FPP), including the final product release if different from the manufacturer. Alternative sites should be also declared here**.** All manufacturing sites involved in the manufacturing process of each step of the finished product, stating the role of each including quality control / in-process testing sites should be listed. (Add as many rows as necessary
Name: Company name: Address: Country: Telephone: Telefax: E-Mail:	
1.17.2	Name(s) and physical address(es) of the manufacturer(s) of the active pharmaceutical ingredient(s) (API) (Add as many rows as necessary) All manufacturing sites involved in the manufacturing process of each source of active substance, including quality control / in-process testing sites should be listed.
Name: Company name: Address: Country: Telephone: Telefax: E-Mail:	
1.18	Name and address (physical and postal) of the Brokers and Suppliers (if applicable)
Name:	

ANNEX II: PRODUCT REGISTRATION APPLICATION FORM

Company name: Address: Country: Telephone: Telefax: E-Mail:	
1.19	Name and address (physical and postal) of the person or company responsible for Pharmacovigilance
Name: Company name: Address: Country: Telephone: Telefax: E-Mail:	
1.20	State the reference/monograph standard such as British Pharmacopeia, United States Pharmacopeia, Ph. Eur, Japanese Pharmacopeia, In-house monograph etc. used for Finished Medicinal Product.
1.21	Qualitative and Quantitative composition of the active substance(s) and excipient(s) A note should be given as to which quantity the composition refers (e.g. 1 capsule).

Name of active ingredient(s)*	Quantity / dosage unit	Unit of measure	Reference/ monograph standard	
1.				
2.				
3.				
etc.				
Name Excipient(s)				
1.				
2.				
3				
etc.				
Note: * Only one name for each substance should be given in the following order of priority: INN**, Pharmacopoeia, common name, scientific name ** The active substance should be declared by its recommended INN, accompanied by its salt or hydrate form if relevant.				

ANNEX II: PRODUCT REGISTRATION APPLICATION FORM

Details of averages should not be included in the formulation columns but should be stated below: - Active substance(s): - Excipient(s):	
1.22	Name and address (physical and postal) of the Contract Research Organisation(s) where the clinical studies of the product were conducted or name and address of laboratory where comparative dissolution studies in support of bio-waiver were conducted. (If applicable)
Name: Company name: Address: Country: Telephone: Telefax: E-Mail:	

2.0 DECLARATION BY AN APPLICANT

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

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

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

I further agree that I am obliged to follow the requirements of Rwanda FDA Legislations and Regulations which are applicable to Humana Medicines.

I also consent to the processing of information provided to Rwanda FDA.

It is hereby confirmed that fees have been paid according to the Rwanda FDA regulations and a proof of payment is enclosed in the dossier.

Name: ……..…….
Position in the company:……
Signature: ……..……

ANNEX II: PRODUCT REGISTRATION APPLICATION FORM

Date:……..
Official stamp:……..

ANNEX III: QUALITY INFORMATION SUMMARY (QIS)

FOREWORD

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

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

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

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

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

ANNEX III: QUALITY INFORMATION SUMMARY (QIS)

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

ANNEX III: QUALITY INFORMATION SUMMARY (QIS)

(b) Administrative Summary:

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

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

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

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

Indicate which option applies for the submission of API information:

Name of API Manufacturer:	
Full details in the PD Open part DMF version number_____ Restricted part DMF version number_____ Identifier of current module 3.2.S: _____	

ANNEX III: QUALITY INFORMATION SUMMARY (QIS)

Name of API manufacturer:	
□	Full details in the PD Open part DMF version number_____ Restricted part DMF version number_____ Identifier of current module 3.2.S: _____ Option 1.
□	Certificate of suitability to the European Pharmacopoeia (CEP) Option 2.
□	Confirmation of API WHO prequalification document: Option 3
□	Active pharmaceutical ingredient master file (APIMF) procedure: APIMF number assigned (if known): _____ ; version number(s) including amendments (and/or date(s)) of the open part: _____ ; version number(s) including amendments (and/or date(s)) of the restricted part: : _____. Option 4.

2.3.S.2 Manufacture (name, manufacturer)

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

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

Name and address (including block(s)/unit(s))	Responsibility	API-PQ number /APIMF/CEP number (if applicable)	Letter of access provided?

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

a) Name of starting material:

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

ANNEX III: QUALITY INFORMATION SUMMARY (QIS)

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

2.3.S.4.1 Specification (name, manufacturer)

API specifications *of the FPP manufacturer*:

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

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

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

2.3.S.7 Stability (name, manufacturer)

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

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

Container closure system	**Storage statement**	**Re-test period***

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

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

ANNEX III: QUALITY INFORMATION SUMMARY (QIS)

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

Name of API:	
Name of API manufacturer:	

□	Full details
□	WHO collaborative procedure
□	SRA Abridged procedure
□	Rwanda FDA Mutual Recognition
□	EU Article 58 procedure

2.3.P.1 Description and Composition of the FPP

a) Description of the FPP:
b) Composition of the FPP:

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

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

ANNEX III: QUALITY INFORMATION SUMMARY (QIS)

Component and quality standard (and grade, if applicable)	Function	Strength (label claim)					
		Quant. per unit or per mL	%	Quant. per unit or per mL	%	Quantity per unit or per mL	%
Total							

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

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

2.3.P.2.2.1 Formulation Development

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

Summary of batch numbers:

Batch number(s) of the FPPs used in

ANNEX III: QUALITY INFORMATION SUMMARY (QIS)

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

Summary of formulations and discussion of any differences:

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

ANNEX III: QUALITY INFORMATION SUMMARY (QIS)

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

2.3.P.3 Manufacture

2.3.P.3.1 Manufacturer(s)

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

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

2.3.P.3.2 Batch Formula

ANNEX III: QUALITY INFORMATION SUMMARY (QIS)

Largest intended commercial batch size:

Other intended commercial batch sizes:

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

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

ANNEX III: QUALITY INFORMATION SUMMARY (QIS)

Component and quality standard (and grade, if applicable)	Quantity per batch (e.g. kg/batch)	Quantity per batch (e.g. kg/batch)	Quantity per batch (e.g. kg/batch)
Subtotal 2			
Total			

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

a) Flow diagram of the manufacturing process:

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

2.3.P.3.4 Controls of Critical Steps and Intermediates

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

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

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

2.3.P.3.5 Process Validation and/or Evaluation

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

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

2.3.P.5 Control of FPP

ANNEX III: QUALITY INFORMATION SUMMARY (QIS)

2.3.P.5.1 Specification(s)

a) Specification(s) for the FPP:

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

2.3.P.7 Container Closure System

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

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

2.3.P.8 Stability

ANNEX III: QUALITY INFORMATION SUMMARY (QIS)

2.3.P.8.1 Stability Summary and Conclusions

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

Container closure system	Storage statement	Shelf-life

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

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

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

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

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

ANNEX III: QUALITY INFORMATION SUMMARY (QIS)

	closure system>	
Tests and acceptance criteria	Description	
	Moisture	
	Impurities	
	Assay	
	etc.	
Testing Frequency		
Container Closure System(s)		

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

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

ANNEX III: QUALITY INFORMATION SUMMARY (QIS)

2.3.P.8.3 Stability Data

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

WRITTEN COMMITMENTS OF THE MANUFACTURER – Rwanda FDA use

API

If applicable (primary stability study commitment):

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

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

If applicable (commitment stability studies):

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

API option 1 - full details in the PD (ongoing stability study commitment)

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

ANNEX III: QUALITY INFORMATION SUMMARY (QIS)

API option 2 - CEP

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

FPP

If applicable (primary stability study commitment):

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

If applicable (commitment stability studies):

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

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

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

ANNEX III: QUALITY INFORMATION SUMMARY (QIS)

Ongoing stability study commitment

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

If applicable (validation of production batches)

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

Change History

Date of preparation of original QIS:

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

Annex IV: Expert Declaration Form

I, the undersigned, declare that I have:

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

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

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

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

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

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

.....

.....

.....

.....

ANNEX V: Letter of Access to CEP

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

Rwanda Food and Drugs Authority
P.O. Box 84 Kigali
Rwanda

Dear Sir/Madam,

Subject: Authorization to access Certificate of Suitability (CEP)

Reference is made to the above subject matter.

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

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

(Name of company or individual)

The API is manufactured by:

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

A formal agreement exists between the applicant of the medicine and the manufacturer of the API, which ensures that information will be communicated between them. Except as permitted by the Rwanda FDA guidelines relating to changes to medicines, such changes will not be made

ANNEX V: Letter of Access to CEP

to the API to be used in manufacture of the medicine destined to be distributed in Rwanda before written approval is granted by the Rwanda FDA.

In addition, we commit that we will inform Rwanda FDA in the event that the CEP is withdrawn.

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

Any questions arising from Rwanda FDA evaluation of this CEP should be forwarded to:

(*Name and address*)

Yours faithfully

{Signature of Company Representative}

{Name}

{Position in Company}

{Date}

ANNEX VI: LETTER OF ACCESS TO APIMF

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

Rwanda Food and Drugs Authority

P.O.Box 84 Kigali

Rwanda

Dear Sir/Madam,

Subject: Authorization to access Active Pharmaceutical Ingredient Master File

Reference is made to the above subject matter.

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

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

(Name of company or individual)

The substance is manufactured by:

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

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

ANNEX VI: LETTER OF ACCESS TO APIMF

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

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

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

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

{Name and address}

Yours faithfully

{Signature of Company Representative}

{Name}

{Position in Company}

{Date}

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

Summary of product information:

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

2.3.S ACTIVE PHARMACEUTICAL INGREDIENT (API))

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

Name of API:	
Name of API manufacturer:	

□	Full details in the PD: • Summaries of the full information should be provided under the appropriate sections; see Section 3.2.S in the Quality guideline.
□	Certificate of suitability to the European Pharmacopoeia (CEP): is a written commitment provided that the applicant will inform Rwanda FDA in the event that the CEP is withdrawn and has acknowledged that withdrawal of the CEP will require additional consideration of the API data requirements to support the dossier: □ yes, □ no;

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

	a copy of the most current CEP (with annexes) and written commitment should be provided *Module 1*; the declaration of access should be filled out by the CEP holder on behalf of the FPP manufacturer applicant to Rwanda FDA who refers to the CEP; and summaries of the relevant information should be provided under the appropriate sections (e.g. S.1.3 S.3.1, S.4.1 through S.4.4, S.6 and S.7; see Quality guideline). .
□	Active pharmaceutical ingredient pre-qualified by WHO Provide evidence from WHO
□	Active pharmaceutical ingredient master file (APIMF): A copy of the letter of access should be provided in *Module 1*; and summaries of the relevant information from the Open part should be provided under the appropriate sections; see Section 3.2. in the Quality guideline

2.3.S.1 General Information

2.3.S.1.1 Nomenclature

(a) (Recommended) International Non-proprietary name (INN):

(b) Compendial name, if relevant:

(c) Chemical name(s):

(d) Company or laboratory code:

(e) Other non-proprietary name(s) (e.g. national name, USAN, BAN):

(f) Chemical Abstracts Service (CAS) registry number:

2.3.S.1.2 Structure

(a) Structural formula, including relative and absolute stereochemistry:

(b) Molecular formula:

(c) Relative molecular mass:

2.3.S.1.3 General Properties

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

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

(b) Solubilities:

In common solvents:

Quantitative aqueous pH solubility profile (pH 1 to 6.8) at 37^{0}C:

Medium (e.g. pH 4.5 buffer)	**Solubility (mg/ml)**
pH 1.2	
pH 4.5	
pH 6.8	

Dose/solubility volume calculation:

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

Polymorphic form:

Solvate:

Hydrate:

(d) Other:

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

2.3.S.2 Manufacture

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

2.3.S.2.1 Manufacturer(s)

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

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

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

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

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

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

(c) Alternate processes and explanation of their use:

(d) Reprocessing steps and justification:

2.3.S.2.3 Control of Materials

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

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

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

(c) Where the API(s) and the starting materials and reagents used to manufacture the API(s) are

without risk of transmitting agents of animal spongiform encephalopathies, a letter of attestation confirming this can be found in:

2.3.S.2.4 Controls of Critical Steps and Intermediates

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

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

2.3.S.2.5 Process Validation and/or Evaluation

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

2.3.S.2.6 Manufacturing Process Development

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

2.3.S.3 Characterisation

2.3.S.3.1 Elucidation of Structure and other Characteristics

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

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

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

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

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

(e) Other characteristics:

2.3.S.3.2 Impurities

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

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

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

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

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

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

(b) Basis for setting the acceptance criteria for impurities:

(i) Maximum daily dose (i.e. the amount of API administered per day) for the API, corresponding to ICH Reporting/Identification/Qualification

Thresholds for the API-related impurities and the concentration limits (ppm) for the process-related impurities (e.g. residual solvents):

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

	<solvent 2>, etc.	

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

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

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

**e.g. comparative bioavailability or bio-waiver studies, stability

(iii) Justification of proposed acceptance criteria for impurities:

2.3.S.4 Control of the API

2.3.S.4.1 Specification

(a) API specifications *of the FPP manufacturer*:

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

Identification		
Impurities		
Assay		
etc.		

2.3.S.4.2 Analytical Procedures

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

2.3.S.4.3 Validation of Analytical Procedures

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

(b) Summary of verification information on compendia methods

2.3.S.4.4 Batch Analyses

(a) Description of the batches:

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

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

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

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

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

2.3.S.4.5 Justification of Specification

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

2.3.S.5 Reference Standards or Materials

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

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

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

2.3.S.6 Container Closure System

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

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

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

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

2.3.S.7 Stability

2.3.S.7.1 Stability Summary and Conclusions

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

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

Stress condition	Treatment	Results (e.g. including discussion whether mas balance is observed)
Base		
Other		

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

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

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

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

Test	**Results**
Description	
Moisture	
Impurities	
Assay	
etc.	

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

Container closure system	**Storage statement**	**Re-test period***

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

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

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

Parameter	**Details**

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

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

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

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

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

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

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

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

2.3.S.7.3 Stability Data

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

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

2.3.P FINISHED PHARMACEUTICAL PRODUCT (FPP))

2.3.P.1 Description and Composition of the FPP

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

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

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

(ii) Composition of all *components purchased as mixtures*

(e.g. colourants, coatings, capsule shells, imprinting inks):

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

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

2.3.P.2 Pharmaceutical Development

2.3.P.2.1 Components of the FPP

2.3.P.2.1.1 Active Pharmaceutical Ingredient

(a) Discussion of the:

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

(ii) key physicochemical characteristics (e.g. water content,

solubility, particle size distribution, polymorphic or solid state form) of the API(s) that can influence the performance of the FPP:

(iii) for fixed-dose combinations, compatibility of APIs with each other:

2.3.P.2.1.2 Excipients

(a) Discussion of the choice of excipients listed in 2.3.P.1 (e.g. their concentrations, their

characteristics that can influence the FPP performance):

2.3.P.2.2 Finished Pharmaceutical Product

2.3.P.2.2.1 Formulation Development

(a) Summary describing the development of the FPP (e.g.

route of administration, usage, optimization of the formulation, etc.):

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

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

(i) Summary of batch numbers:

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

(ii) Summary of formulations and discussion of any differences:

Component an	**Relevant batches**							
Qualit y standard (e.g. NF, B Ph.Eur, in-house	**Comparative bioavailability or bio waiver**		**Stability**		**Process validation**		**Commercial (2.3.P.1)**	
	<Batch nos. an sizes>		**<Batch nos. an sizes>**		**<Batch nos. an sizes>**		**<Batch nos. an sizes>**	
	Theor. quantity per batch	**%**	**Theor. quantity p batch**	**%**	**Theor. quantity p batch**	**%**	**Theor. quantity p batch**	**%**
<complete with appropriate title e.g. Core tablet, Contents of capsule, Powder								

for injection>								
Subtotal 1								
<complete with appropriate title e.g. Film-coating >								
Subtotal 2								
Total								

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

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

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

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

2.3.P.2.2.2 Overages

(a) Justification of overages in the formulation(s) described in 2.3.P.1:

2.3.P.2.2.3 Physicochemical and Biological Properties

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

(e.g. pH, ionic strength, dissolution, particle size distribution, polymorphism, rheological properties):

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

2.3.P.2.3 Manufacturing Process Development

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

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

2.3.P.2.4 Container Closure System

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

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

2.3.P.2.5 Microbiological Attributes

(a) Discussion of microbiological attributes of the FPP (e.g.

preservative effectiveness studies):

2.3.P.2.6 Compatibility

(a) Discussion of the compatibility of the FPP (e.g. with

reconstitution diluent(s) or dosage devices, co-administered FPPs):

2.3.P.3 Manufacture

2.3.P.3.1 Manufacturer(s)

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

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

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

2.3.P.3.2 Batch Formula

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

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

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

(a) Flow diagram of the manufacturing process:

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

(c) Justification of reprocessing of materials:

2.3.P.3.4 Controls of Critical Steps and Intermediates

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

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

2.3.P.3.5 Process Validation and/or Evaluation

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

2.3.P.4 Control of Excipients

2.3.P.4.1 Specifications

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

2.3.P.4.2 Analytical Procedures

(a) Summary of the analytical procedures for supplementary tests:

2.3.P.4.3 Validation of Analytical Procedures

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

2.3.P.4.4 Justification of Specifications

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

2.3.P.4.5 Excipients of Human or Animal Origin

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

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

(b) CEP(s) demonstrating TSE-compliance can be found in: (page and volume)

2.3.P.4.6 Novel Excipients

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

2.3.P.5 Control of FPP

2.3.P.5.1 Specification(s)

Specification(s) for the FPP:

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

2.3.P.5.2 Analytical Procedures

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

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

2.3.P.5.3 Validation of Analytical Procedures

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

2.3.P.5.4 Batch Analyses

(a) Description of the batches:

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

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

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

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

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

2.3.P.5.5 Characterisation of Impurities

(a) Identification of potential and actual impurities:

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

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

(c) Basis for setting the acceptance criteria for impurities:

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

Maximum daily dose for the API:	**<x mg/day>**	
Test	**Parameter**	**ICH threshold of concentration limit**
Degradation product	Reporting Threshold	

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

	Identification Threshold	
	Qualification Threshold	
Process-related impurities	<solvent 1>	
	<solvent 2>, etc.	

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

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

(iii) Justification of proposed acceptance criteria for impurities:

2.3.P.5.6 Justification of Specification(s)

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

2.3.P.6 Reference Standards or Materials

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

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

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

2.3.P.7 Container Closure System

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

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

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

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

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

2.3.P.8 Stability

2.3.P.8.1 Stability Summary and Conclusions

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

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

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

Storage Condition (°C, % RH)	Strength an batch number	Batch size	Container closure system	Completed (an proposed)testing?? te intervals	

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

Test	Results
Description	
Moisture	
Impurities	
Assay	
etc.	

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

Container closure system	Storage statement	Shelf-life

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

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

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

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

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

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

Container Closure System(s)	

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

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

2.3.P.8.3 Stability Data

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

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

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

2.3.A APPENDICES

2.3.A.1 Facilities and Equipment

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

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2.3.A.2 Adventitious Agents Safety Evaluation

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

2.3.A.3 Excipients

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

2.3.R REGIONAL INFORMATION

2.3.R.1 Production Documentation

2.3.R.1.1 Executed Production Documents

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

2.3.R.1.2 Master Production Documents

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

2.3.R.2 Analytical Procedures and Validation Information

ANALYTICAL PROCEDURES AND VALIDATION INFORMATION SUMMARIES

ATTACHMENT NUMBER:	

HPLC Method Summary		**Volume/Page:**	
Method name:			
Method code:		**Version and/or Date:**	
Column(s) / temperature (if other than ambient):			
Mobile phase (specify gradient program, if applicable):			
Detector (and wavelength, if applicable):			

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Flow rate:	
Injection volume:	
Sample solution concentration (expressed as mg/ml, let this be termed "A"):	
Reference solution concentration (expressed as mg/ml and as % of "A"):	
System suitability solution concentration (expressed as mg/ml and as % of "A"):	
System suitability tests (tests and acceptance criteria):	
Method of quantification (e.g. against API or impurity reference standard(s)):	
Other information (specify):	
ATTACHMENT NUMBER:	

Validation Summary		**Volume/Page:**			
Analytes:					
Typical retention times (RT)					
Relative retention times ($RT_{Imp.}/RT_{API\ or\ Int.\ Std.}$):					
Relative response factor ($RF_{Imp.}/RF_{API}$):					
Specificity:					
Linearity / Range:	Number of concentrations: Range (expressed as % "A"): Slope: Y-intercept: Correlation coefficient (r^2) :				
Accuracy:	Conc.(s) (expressed as % "A"): Number of replicates: Percent recovery (avg/RSD):				
Precision / Repeatability: (intra-assay precision)	Conc.(s) (expressed as % "A"): Number of replicates: Result (avg/RSD):				

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

Precision / Intermediate Precision: (days/analysts/equipment)	Parameter(s) altered: Result (avg/RSD):	
Limit of Detection (LOD): (expressed as % "A")		
Limit of Quantitation (LOQ): (expressed as % "A")		
Robustness:	Stability of solutions: Other variables/effects:	
Typical chromatograms or spectra may be found in:		
Company(s) responsible for method validation:		
Other information (specify):		

ANNEX IX: BIOWAIVER APPLICATION FORM

General Instructions:

Please review all the instructions thoroughly and carefully prior to completing the Bioequivalence Trial Information Form (BTIF).

Provide as much detailed, accurate and final information as possible. Note that the greyed areas are NOT to be filled in by the applicant but are for Rwanda FDA use ONLY!

Please state the exact location (Annex number) of appended documents in the relevant sections of the BTIF. For example, in **section 3.4.3.1** under **point b)**, indicate in which Annex (number) the Certificate of Analysis can be found. This procedure must be followed throughout the entire document where location of annexed documents is requested.

Before submitting the completed BTIF, kindly check that you have provided all requested information and enclosed all requested documents.

Should you have any questions regarding this Form, please contact Rwanda FDA.

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

ASSESSMENT REPORT FOR GENERIC FINISHED PHARMACEUTICAL PRODUCTS (FPPS) NOT REGISTERED IN ICH REGIONS OR RELATED COUNTRIES

BIOEQUIVALENCE PART OF A NEW DOSSIER

Reference of the session		
Date		
Type of product		
Type of dossier	**EFFICACY**	
Type of submission	**NEW**	
First assessor	Name	Signature

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Second assessor	Name	Signature
Quality assessor (e.g., when dissolution profiles are submitted for comparison of the compositions of clinical, stability and validation batches, or a bio waiver for additional strengths is requested.)	Name	Signature
Reference Number		
Date of the submission		
Number of binders		
SPC , PIL submitted	(state location in submission)	
SPC, PIL, Package Labelling acceptable	Yes:_____// No:_____	
Proprietary Product Name (if relevant)	*..	
International Non-proprietary Name (INN) of the Active Pharmaceutical Ingredient (API), strength, pharmaceutical form.	*..	
Conclusion of the assessment	**ACCEPTED (no outstanding issues)** **ADDITIONAL DATA REQUESTED** **REJECTED** ***(please delete the wrong entries)***	
Name and complete address of the supplier (Applicant of the dossier)	*..	
Name and address of the Contract Research Organisation(s) where the clinical studies proving efficacy and safety of the product were conducted. *(Add as much rows as necessary)*	*..	

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This product assessment report should be written in clear unambiguous language referring to deficiencies or lack of data submitted, as communication with the manufacturer may result from the assessment.

BIOEQUIVALENCE TRIAL INFORMATION

1 SUMMARY

1.1 ***Summary of bioequivalence studies performed***

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

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

(State the location of the master formulae in the quality part of the submission)

(Tabulate the composition of each product strength using the table below. For solid oral dosage forms the table should contain only the ingredients in tablet core /contents of a capsule. A copy of the table should be filled in for the film coating / hard capsule, if any.

Important: If the formulation proposed for marketing and those used for bioequivalence studies are not identical, copies of this table should be filled in for each formulation with clear identification in which bioequivalence study the respective formulation was used)

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

2. HAS COMPARATIVE BIOAVAILABILITY DATA BEEN SUBMITTED FOR ALL STRENGTHS?

(If comparative bioavailability data has not been submitted for all strengths, provide a scientific justification for not submitting such data; append copies of all references cited in the justification. Justification should include – but is not limited to – argumentation related to dose-

[1] Bioequivalence batches should be at least of pilot scale (10% of production scale or 100,000 capsules/tablets whichever is the greater) and manufacturing method should be the same as for production scale.

proportional composition, dose-linearity of pharmacokinetics (Cmax and AUC,), discriminatory (with regard to bioavailability differences) power of dissolution tests employed).

Sections 3.0 – 11.0 below should be copied and completed separately for each bioequivalence study performed.

3.0 CLINICAL STUDY REPORT

Study number:

Study Title:

Location of Study Protocol:

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

3.1 ETHICS

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

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

3.2 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

a) Name of principal investigator(s) *(State location of c.v. in the submission)*

b) Clinical Facility *(Name and full mailing address)*

c) Clinical Laboratories *(Name and full mailing address)*

d) Analytical Laboratories *(Name and full mailing address)*

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e) Company performing pharmacokinetic/statistical analysis *(Name and full mailing address)*

3.3 STUDY OBJECTIVES

Briefly state the study objectives.

3.4 INVESTIGATIONAL PLAN

3.4.1 Overall Study Design and Plan – Description

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

sentences)

3.4.2 Selection of Study Population

3.4.2.1 Inclusion Criteria

3.4.2.2 Exclusion Criteria

(List the exclusion criteria applied to subjects)

3.4.2.3 Removal of Trial subjects from Trial or Assessment

(a) Number of subjects enrolled in the study

(All subjects including alternates, withdrawals, and dropout

(b) Withdrawals

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

3.4.2.4 Health Verification

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

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

b) Indicate when tests were performed

c) Study site normal values

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

d) Report any results that were outside of study site normal values

(State location in submission of the summary of anomalous values)

3.4.2.5. **Removal of Trial subjects from Trial or Assessment**

(a) Number of subjects enrolled in the study

(All subjects including alternates, withdrawals, and dropouts)

(b) Alternates

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

(c) Withdrawals/dropouts

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

3.4.3 Products Administered

3.4.3.1 Test Product

(a) Batch number, size and date of manufacture for the test product
(b) Potency (measured content) of test product as a percentage of label claim as per validated assay method

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

3.4.3.2 Comparator (Reference) Product

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

(a) Name and manufacturer of the Comparator product

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

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

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

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

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

(e) Justification of choice of reference product

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

3.4.4 Selection of Doses in the Study

(a) State dose administered

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(Indicate the number of dosage units comprising a single dose, e.g., 400 mg as 1 x 400 mg or 2 x 200 mg tablets)

3.4.5 Selection and Timing of Dose for Each Subject

(a) State volume and type of fluid consumed with dose,
(b) Interval between doses (i.e., length of washout),

(c) Protocol for the administration of food and fluid,

(d) Restrictions on posture and physical activity during the study

3.4.6 Blinding

3.4.6.1 Identify which of the following were blinded. If any of the groups were not blinded, provide a justification for not doing so

a) study monitors: Yes ☐ / No ☐ If No, justify: _____

b) subjects: Yes ☐ / No ☐ If No, justify: _____

c) analysts: Yes ☐ / No ☐ If No, justify: _____

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

3.4.7 Drug Concentration Measurements

3.4.7.1 Biological fluid(s) sampled

3.4.7.2 Sampling Protocol

(a) Number of samples collected per subject

(b) Volume of fluid collected per sample

(c) Total volume of fluid collected per subject per phase of the study

(d) List the study sampling times

(e) Identify any deviations from the sampling protocol (State location of summary in the submission)

(Describe and explain reasons for deviations from sampling protocol. Comment on impact on study. Indicate whether the deviations were accounted for in the pharmacokinetic analysis)

3.4.7.3 Sample Handling

(a) Describe the method of sample collection

(b) Describe sample handling and storage procedures

3.5 COMMENTS FROM REVIEW OF SECTION 3.0 – RWANDA FDA USE ONLY

4.0 TRIAL SUBJECTS

4.1 Demographic and Other Baseline Characteristics

(a) Identify study population (i.e., normal, healthy adult volunteers or patients)
(b) Summary of ethnic origin and gender of subjects
(c) Identify subjects noted to have special characteristics and state notable characteristics
(d) (e.g., fast acetylators of debrisoquine)
(e) Range and mean age ± SD of subjects
(f) Range and mean height and weight ± SD of subjects
(g) Identify subjects whose ratio is not within 15% of the values given on a standard height/weight table

4.2 Subjects who smoke

(a) Number of smokers included in the study;
(b) Indicate how many cigarettes smoked per day per subject;

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(c) Comment on the impact on study.

4.3 COMMENTS FROM REVIEW OF SECTION 4.0 – RWANDA FDA USE ONLY

5.0 PROTOCOL DEVIATIONS

5.1 Protocol deviations during the clinical study

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

5.2 COMMENTS FROM REVIEW OF SECTION 5.0 – RWANDA FDA USE ONLY

6.0 SAFETY EVALUATION

6.1 Identify adverse events observed

(List any adverse events by subject number. State whether a reaction occurred following administration of the test or reference product, identify any causal relationships, and note any treatments required. State location of this summary in the submission)

(Discuss the implications of the observed adverse events with respect to bioequivalence)

6.2 COMMENTS FROM REVIEW OF SECTION 6.0 – RWANDA FDA USE ONLY

7.0 EFFICACY EVALUATION –

Efficacy Results and Tabulations of Individual Trial Subjects Data

7.1 Presentation of Data

(a) State location in submission of tables of mean and individual subject concentrations

(b) State location in submission of (mean and individual) linear and semi-logarithmic subject drug concentration vs. time plots

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7.2. Pharmacokinetic (PK) Parameters

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

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

(c) Complete the table below

	Test			**Reference**		
Parameter	Arithmetic mean	Standard deviation	Inter individual coefficient of variation (%)	Arithmetic mean	Standard deviation	Inter individual coefficient of variation (%)
AUC_T(Unit)						
AUC_I (units)						
C_{max} (units)						
T_{max} (units)						
$T_{½}$ (units)						

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

(b) Ratio of AUC_T to AUC_I _____

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

7.3 Statistical Analysis

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

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

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

(b) Period and/or sequence effects

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

(c) Comparison of the results

(Compare the results, including mean values, inter- and intra-individual variability, of this study with published results (literature, product information of reference product (innovator), WHOPARs), and copies of the references used should be appended to this document)

7.4 DISCUSSION OF RESULTS

(State location of the discussion of the results in the submission. If the discussion currently included in the study report does not include comparisons of results, including inter- and

intraindividual variability, of this study with published results (literature, product information of reference product (innovator), such a discussion should be provided here and copies of the references used should be appended to this document)

7.5 COMMENTS FROM REVIEW OF SECTION 7.0 – RWANDA FDA USE ONLY

8.0 ANALYTICAL STUDY REPORT

8.1 Analytical Technique

8.1.1 Analytical protocol
(State the location of the analytical protocol)
8.1.2 Identify analyte(s) monitored

8.1.3 Comment about source and validity of reference standard

8.1.4 Identify analytical technique employed

8.1.5 Identify method of detection

8.1.6 Identify internal standard

8.1.7 If based on a published procedure, state reference citation

8.1.8 Identify any deviations from protocol

8.1.9 Dates of subject sample analysis

8.1.10 Longest period of subject sample storage

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

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

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8.2 Standard Curves

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

(a) List number and concentration of calibration standards used
(b) State number of curves run during the study
(c) Summarize descriptive data including slope, intercept, correlation coefficients
(d) Describe the regression model used including any weighting
(e) State the limit of quantitation (LOQ)

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

8.3 Quality Control Samples

(a) Identify the concentrations of the QC samples, their date of preparation and the storage conditions employed prior to their analysis
(b) State the number of QC samples in each analytical run per concentration

8.4 Precision and Accuracy

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

8.5 Repeat Analysis

(a) List repeats by sample identification and include the following information for each repeat: initial value; reason for repeat; repeat value(s); accepted value; and reason for acceptance;
(b) Report the number of repeats as a percentage of the total number samples assayed

8.6 Chromatograms

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(State the location in the submission where the sample chromatograms can be found. The chromatograms should be obtained from a minimum of two analytical batches and include at least 20% of the subjects, up to a maximum of five. A complete set includes standards, QC samples, pre-dose and post-dose subject samples for both phases. Each chromatogram should be clearly labelled with respect to the following: date of analysis; subject ID number; study period; sampling time; analyte; standard or QC, with concentration; analyte and internal standard peaks; peak heights and/or areas)

8.7 COMMENTS FROM REVIEW OF SECTION 8.0 – RWANDA FDAUSE ONLY

9.0 ANALYTICAL VALIDATION REPORT

9.1 Precision and Accuracy

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

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

9.2 Stability

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

(a) Summarize data on long-term storage stability
(b) Summarize data on freeze-thaw stability
(c) Summarize data on bench top stability
(d) Summarize data on auto sampler storage stability
(e) Summarize data from any other stability studies conducted

(e.g., stock solution stability)

9.3 Specificity

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

9.4 Matrix effect (in case of MS detection)

(Methods to verify the matrix effect & results)

9.5 Recovery

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

9.6 COMMENTS FROM REVIEW OF SECTION 9.0 – RWANDA FDA USE ONLY

10.0 QUALITY ASSURANCE

10.1 Internal quality assurance methods

(State locations in the submission where internal quality assurance methods and results are described for each of study sites (see 3.2 b-d)

10.2 Monitoring, Auditing, Inspections

(Provide a list of all monitoring and auditing reports of the study, and of recent inspections of study sites by regulatory agencies. State locations in the submission of the respective reports for each of study sites (see 3.2 b-d)

10.3 COMMENTS FROM REVIEW OF SECTION 10 – Rwanda FDA USE ONLY

CONCLUSIONS AND RECOMMENDATIONS – Rwanda FDA USE ONLY

POINTS TO BE COMMUNICATED TO THE MANUFACTURER

(b) General remark, if applicable

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

(c) Overall conclusion

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

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

RECOMMENDATIONS FOR INSPECTION

Biopharmaceutics Classification System (BCS)

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

Rwanda FDA has identified the Active Pharmaceutical Ingredients (APIs) that are eligible for a BCS-based bio waiver application. Therefore, <u>in some cases</u> it is not necessary to provide data to support the BCS classification of the respective API(s) in the application i.e. data supporting the drug substance solubility or permeability class.

General Instructions*:*

- Please review all the instructions thoroughly and carefully prior to completing the current Application Form.
- Provide as much detailed, accurate and final information as possible

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- Please enter the data and information directly following the greyed areas.
- Please enclose the required documentation in full and state in the relevant sections of the Application Form the exact location (Annex number) of the appended documents.
- Please provide the document as an MS Word file
- Do not paste snap-shots in the document
- Please enclose the required documentation in full and state in the relevant sections of the Application Form the exact location (Annex number) of the appended document.
- The appended electronic document should be clearly identified in their file names, which should include the product name and Annex number.
- Before submitting the completed Application Form, kindly check that you have provided all requested information and enclosed all requested documents.
- Should you have any questions regarding this procedure, please contact Rwanda FDA.

The signed paper version of this Bio waiver Application Form together with Annexes (and their electronic copies on CD-ROM) should be included to the bioequivalence part of the submitted dossier and sent by surface mail to Rwanda FDA.

1.0 Administrative data

1.1 ***Trade name of the test product***

1.2	***INN of active ingredient(s)***
	< Please enter information here >
1.3	***Dosage form and strength***
	< Please enter information here >

1.1 ***Product EAC Reference number*** *(if product dossier has been*

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accepted for EAC assessment)
< Please enter information here >
1.5 Name of applicant and official addresses
< Please enter information here >
1.2 Name of manufacturer of finished product and full physical address of the manufacturing site
< Please enter information here >
1.3 Name and address of the laboratory or Contract Research Organisation(s) where the BCS-base bio waiver dissolution studies were conducted.
< Please enter information here >

2.0 Test product

2.1 Tabulation of the composition of the formulation(s) proposed for marketing and those used for comparative dissolution studies

- ☐ Please state the location of the master formulae in the specific part of the dossier of the submission.
- ☐ Tabulate the composition of each product strength using the table 2.1.1
- ☐ For solid oral dosage forms the table should contain only the ingredients in

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tablet core or contents of capsule. A copy of the table should be filled in for the film coating/hard gelatine capsule, if any.

□ Bio waiver batches should be at least of pilot scale (10% of production scale or 100,000 capsules or tablets whichever is greater) and manufacturing method should be the same as for production scale.

Please note: If the formulation proposed for marketing and those used for comparative dissolution studies are not identical, copies of this table should be filled in for each formulation for clear identification in witch study the respective formulation was used.

2.1.1 ***Composition of the batches used for comparative dissolution studies***

Batch number	
Batch size (number of unit doses)	
Date of manufacture	
Comments, if any	

Comparison of unit dose compositions
(duplicate this table for each strength, if compositions are different)

Ingredients (Quality standard)	Unit dose (mg)	Unit dose (%)		
Equivalence of the compositions or justified differences				

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

This information should be cross-referenced to the location of certificate of analysis (CoA) in this bio waiver submission.

< Please enter information here >

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COMMENTS FROM REVIEW OF SECTION 2.0 - Rwanda FDA USE ONLY

2.0 Comparator product

3.1 ***Comparator product***

Please enclose a copy of product labelling (summary of product characteristics), as authorized in country of purchase, and translation into English, if appropriate.

3.2 ***Name and manufacturer of the comparator product (Include full physical address of the manufacturing site)***

< Please enter information here >

3.3 Qualitative (and quantitative, if available) information on the composition of the comparator product

Please tabulate the composition of the comparator product based on available information and state the source of this information.

3.3.1 ***Composition of the comparator product used in dissolution studies***

Batch number	
Expiry date	

Comments, if any

Ingredients and reference standards used	Unit dose (mg)	Unit dose (%)

3.4 ***Purchase, shipment and storage of the comparator product***

Please attach relevant copies of documents (e.g. receipts) proving the stated conditions.

< Please enter information here >

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

This information should be cross-referenced to the location of certificate of analysis (CoA) in this bio waiver submission.

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< Please enter information here >
COMMENTS FROM REVIEW OF SECTION 3.0 - Rwanda FDA USE ONLY

3.0 Comparison of test and comparator products

3.1 ***Formulation***
4.1.1 ***Identify any excipients present in either product that are known to impact on in vivo absorption processes*** A literature-based summary of the mechanism by which these effects are known to occur should be included and relevant full discussion enclosed, if applicable.
< Please enter information here >

.2 ***Identify all qualitative (and quantitative, if available) differences between the compositions of the test and comparator products***
The data obtained and methods used for the determination of the quantitative composition of the comparator product as required by the guidance documents should be summarized here for assessment
< Please enter information here >
4.3 ***Provide a detailed comment on the impact of any differences between the compositions of the test and comparator products with respect to drug release and in vivo absorption***
< Please enter information here >
COMMENTS FROM REVIEW OF SECTION 4.0 - Rwanda FDA USE ONLY
4.0 Comparative in vitro dissolution

RWANDA FDA

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Information regarding the comparative dissolution studies should be included below to provide adequate evidence supporting the bio waiver request. Comparative dissolution data will be reviewed during the assessment of the Quality part of the dossier Please state the location of: ☐ the dissolution study protocol(s) in this bio waiver application ☐ the dissolution study report(s) in this bio waiver application ☐ the analytical method validation report in this bio waiver application
< Please enter information here >
5.1 ***Summary of the dissolution conditions and method described in the study report(s)*** Summary provided below should include the composition, temperature, volume, and method of de-aeration of the dissolution media, the type of apparatus employed, the agitation speed(s) employed, the number of units employed, the method of sample collection including sampling times, sample handling, and sample storage. Deviations from the sampling protocol should also be reported

5.1.1 ***Dissolution media: Composition, temperature, volume, and method of de-aeration***
< Please enter information here >

5.1.2 ***Type of apparatus and agitation speed(s) employed***
< Please enter information here >

5.1.3 ***Number of units employed***
< Please enter information here >

5.1.4 ***Sample collection: method of collection, sampling times, sample handling and storage***
< Please enter information here >

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5.1.5 ***Deviations from sampling protocol***
< Please enter information here >

5.1.6 ***Dissolution media: Composition, temperature, volume, and method of de-aeration***
< Please enter information here >
5.2 ***Summarize the results of the dissolution study(s)*** Please provide a tabulated summary of individual and mean results with % CV, graphic summary, and any calculations used to determine the similarity of profiles for each set of experimental conditions.
< Please enter information here >

5.3 ***Provide discussions and conclusions taken from dissolution study(s)*** Please provide a summary statement of the studies performed.
< Please enter information here >

COMMENTS FROM REVIEW OF SECTION 5.0 - Rwanda FDA USE ONLY

6.0 Quality assurance

6.1 ***Internal quality assurance methods*** Please state location in this bio waiver application where internal quality assurance methods and results are described for each of the study sites
< Please enter information here >

6.2 ***Monitoring, Auditing, Inspections*** Provide a list of all auditing reports of the study, and of recent inspections of study sites by regulatory agencies. State locations in this bio waiver application of the respective reports for each of the study sites e.g., analytical laboratory, laboratory where dissolution studies were performed
< Please enter information here >

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COMMENTS FROM REVIEW OF SECTION 6.0 – Rwanda FDA USE ONLY

Declaration
I, the undersigned, certify that the information provided in this application and the attached document is correct and true
Signed on behalf of <company> Date Name and title *< Please enter information here >*

CONCLUSIONS AND RECOMMENDATIONS – Rwanda FDA USE ONLY

ANNEX X: REGISTRATION CERTIFICATE FORMAT

RWANDA FDA
Rwanda Food and Drugs Authority

MEDICINAL PRODUCT REGISTRATION CERTIFICATE

(Made under law No. 003/2018 of 09/02/2018 establishing the Rwanda FDA and determining its mission, organization and functioning in his article 3 and article 8)

Registration number: **********

This is to certify that the Medicine described below has been registered in Rwanda subject to conditions indicated at the back of this certificate.

Brand Name: **********

Name of the Active ingredient(s) and Strength: **********

Therapeutic Indication: **********

Dosage Form and appearance: **********

Pack size and Packaging type: **********

Shelf life in months and Storage statement: **********

Distribution category: **********

Name of Marketing Authorization Holder: ********

Name and address of manufacturer: **********

Name and address of Local Technical Representative: **********

Issue On: *********

Expires on: *********

Dr. Charles KARANGWA
Ag. Director General

ANNEX X: REGISTRATION CERTIFICATE FORMAT

Conditions for human medicinal Product Registration

1. This certificate must be returned to the Authority if canceled, invalidated or if the registered Human Medicinal Product is withdrawn.
2. Any change in the information submitted for the purpose of registration must be notified to the Rwanda FDA within 30 days of the change.
3. This certificate shall be invalid immediately after the expiry date and the Marketing Authorization Holder shall ensure that application for renewal of registration is made 90 days before expiry of registration.
4. Registered Human Medicinal Product cannot be advertised without prior approval of the Authority.
5. The Human Medicinal Product shall comply with all relevant provisions of Rwanda FDA regulations at all times.
6. The Marketing Authorization Holder shall ensure that the Human Medicinal Product complies with Rwandan labelling and packaging requirements at all times.
7. The Marketing Authorization Holder shall ensure that the manufacturing facilities where a registered Human Medicinal Product is produced comply at all times with Rwanda FDA Good Manufacturing Practice requirements.
8. The Marketing Authorization Holder shall notify Rwanda FDA of the change of a Local Technical Representative at all times.
9. The registration of the Human Medicinal Product shall continue to be valid for five (5) years provided that annual retention fee is paid.
10. The Authority reserves the right to withdrawal this certificate when conditions 1 to 7 are contravened and when the risks of using this medicine outweighs the benefits or it is in public interest to do so.