Botswana Medicines Regulatory Authority

BOMRA
MEDICINES REGULATORY AUTHORITY

Approved By: _____

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Date of Approval (DD/MM//YY) _____

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All pages	Removed aspects pertaining to biotechnology derived products	1.0	LM/CTT	18/08/2023
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1) Purpose

These guidelines provide the format and content of applications for registration of drug substances and their corresponding drug products containing synthetic or semi-synthetic origin. They are intended to assist applicants to generate and compile a Common Technical Document for application to register medicines in Botswana.

2) Scope

These guidelines apply to human medicines registration applications containing APIs of synthetic or semi-synthetic origin. The guidelines cover both generic and new medicines. For specific quality requirements for biologicals (e.g. human vaccines, cell based products, blood and blood products) refer to the BoMRA Guideline on Adopted Documents of External Origin (BOMRA/ER/MD/P04/G06).

3) Abbreviations and Definitions

3.1 Abbreviations

For the purpose of these guidelines, the following abbreviations shall apply:

API	Active Pharmaceutical Ingredient
CEP	Certificate of Suitability (Ph. Eur. monograph)
CHMP	Committee for Medicinal Products for Human Use (formally, Committee for Proprietary Medicinal Products) (EU)
CTD	Common Technical Document
EDQM	European Directorate for the Quality of Medicines
EPAR	European public assessment reports
EU	European Union
FPP	Finished Pharmaceutical Product
GCP	Good Clinical Practice
GMO	Genetically Modified Organism
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IPD	Individual Patient Data

IPI	Inactive Pharmaceutical Ingredient
IT	Information technology
MHRA	UK Medicines and Health products Regulatory Authority
MS	Member State
NMRA	National Medicines Regulatory Authority
PDF	Portable document format
PDs	Product Dossiers
PI	Package Insert
PIL	Patient Information Leaflet
PMF	Plasma Master File
QOS	Quality Overall Summary
SADC	Southern African Development Community
SmPC	Summary of Product Characteristics (European)
TGA	Australian Therapeutic Goods Authority
UK	United Kingdom
US FDA	United States Food and Drug Administration
USA	United States of America
WHO	World Health Organization
WHOPAR	World Health Organization public assessment reports

3.2 Definitions

For the purpose of this document, the following definitions shall apply:

3.2.1 Active pharmaceutical ingredient (API) or drug substance – Any substance or mixture of substances used in the manufacture of a pharmaceutical dosage form, and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body.

3.2.2 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. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house (ICH Q7). See also starting materials for synthesis.

3.2.3 Applicant – Means a company or entity registered in terms of the Companies Act and operating in the Republic of Botswana.

3.2.4 Biopharmaceutics Classification System (BCS) highly soluble – An API for which the highest dose recommended by WHO (if the API appears on the WHO Model list of essential medicines) or highest dose strength available on the market as an oral solid dosage form (if the API does not appear on the WHO Model list of essential medicines) is soluble in 250 ml or less of aqueous media over the pH range of 1.2 – 6.8 at 37°C.

3.2.5 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.

3.2.6 Reference product –Pharmaceutical product with which the new product is intended to be interchangeable in clinical practice. The reference product will normally be the innovator product for which efficacy, safety and quality have been established. Where the innovator product is not available, the applicant should consult the medicines regulatory authority for suitable reference product.

3.2.7 Established generic (multisource) product – A multisource product that has been marketed by the applicant or manufacturer associated with the dossier for at least five years and for which at least 10 production batches were produced over the previous year, or, if less than 10 batches were produced in the previous year, not less than 25 batches were produced in the previous three years.

3.2.8 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 or by

WHO, but requires the filing of a dossier. This would include, for example, new PDs and variations to multisource products.

3.2.9 Finished pharmaceutical product (FPP) or drug product – A finished dosage form of a pharmaceutical product, which has undergone all stages of manufacture, including packaging in its final container and labelling.

3.2.10 Generic (multisource) pharmaceutical products – Generic pharmaceutical products are pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent or bioequivalent. Generic products that are therapeutically equivalent are interchangeable.

3.2.11 Innovator pharmaceutical product – Generally, the innovator pharmaceutical product is that which was first authorised for marketing, on the basis of documentation of quality, safety and efficacy.

3.2.12 Manufacturer – A company that carries out operations such as production, packaging, repackaging, labelling and re-labelling of pharmaceuticals.

3.2.13 Officially recognized pharmacopoeia (or compendium) – Those pharmacopoeias recognized in the WHO Prequalification of Medicines Programme (i.e. British Pharmacopoeia (BP), European Pharmacopoeia (Ph.Eur.), The International Pharmacopoeia (Ph.Int.), Japanese Pharmacopoeia (JP), and United States Pharmacopeia (USP)).

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

3.2.15 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.

3.2.16 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.

3.2.17 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.

3.2.18 Starting materials for synthesis – Materials that mark the beginning of the manufacturing process as described in an application or in an API master file (APIMF). A starting material for a synthetic API is a chemical compound of defined molecular structure that contributes to the structure of the API. See also API starting material.

4 Introduction

These guidelines are intended to assist applicants to generate and compile data for application to register medicines in Botswana. Through the ICH process, considerable harmonization has been achieved on the organization of the registration documents with the issuance of the Common Technical Document (CTD) guideline. This recommended format in the CTD guideline for registration applications has become widely accepted by regulatory authorities the world over.

These guidelines provide recommendations on the quality information for the active pharmaceutical ingredients (APIs) and the finished pharmaceutical products (FPPs) that should be submitted to Botswana to support applications for registration. Alternate approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate scientific justification. Applicants should refer to appropriate ICH guidelines for detailed guidance on submission of efficacy and safety data to support applications for registration of new (innovator) medicines.

4.1 Objectives

These guidelines are intended to:

a) Assist applicants in the preparation of the Quality Module of applications for registration by providing clear general guidance on the format of the applications;

b) Fully adopt the modular format of the Common technical document – quality (M4Q) as developed by ICH;

c) Provide guidance on the technical and other general data requirements.

These measures are intended to promote effective and efficient processes for the development of the applications for registration and the subsequent assessment procedures.

4.2 General principles

To facilitate the preparation of the application, this guideline is organized in accordance with the structure of the Common Technical Document – Quality (M4Q) guideline, as developed by ICH.

The content of these guidelines should be read in conjunction with relevant information described in other existing WHO or ICH reference documents and guidelines. The quality of existing APIs and corresponding generic products should not be inferior to new APIs and innovator (comparator) FPPs. Therefore, the principles of the ICH guidelines that are referenced throughout this and other WHO guidelines may also equally apply to existing APIs and generic products.

Scientific literature may be appropriate to fulfill the requirements for some of the information or parameters outlined in these guidelines (e.g. qualification of specified identified impurities). Furthermore, the requirements outlined in certain sections may not be applicable for the proposed API or FPP. In these situations, a summary and the full reference to the scientific literature should be provided or the non-applicability of the requested information should be clearly indicated as such with an accompanying explanatory note.

4.3 Guidance on format

4.3.1 Preparing and organising the Common Technical Document

To facilitate the review of the basic data and to help an evaluator become oriented with the application contents, the display of information should be unambiguous and transparent throughout the CTD.

If additional or supplementary data are submitted, the module(s) should be identified and numbering should follow from the original documentation.

The applicant should not submit the modules that are not used i.e. it is unnecessary to include "not applicable" pages against unused CTD headings.

For new applications, detailed statements justifying the absence of data or specific CTD sections should be provided in the relevant Quality Overall Summary (QOS) and/or Non-Clinical/Clinical Overviews (Module 2.3, 2.4, 2.5). If relevant, justification for empty sections in Module 1 is to be provided in the cover letter.

Acronyms and abbreviations should be defined the first time they are used in each module.

4.3.2 Documentation

4.3.2.1 Electronic review documents

Electronic documents should be submitted in Microsoft Word (required for templates/summaries, e.g. QOS, QIS, BTIF, Biowaiver forms, etc.). Other documentation should be submitted in text-searchable PDF format (e.g., respective dossier files) Guidance on eCTD submissions will be provided in future.

4.4 Presentation of information

Font sizes for text and tables should be of a style and size that are large enough to be easily legible, even after photocopying or when provided electronically. *Arial/Times New Roman 12* point font is preferred for narrative text. The copies, including figures, tables and photos should be clearly legible. Shading and/or coloured filling/background and/or print, e.g. in tables and headers, or across pages, is unacceptable and should be avoided.

Following are recommendations for the presentation of the information in the Quality Module for different scenarios that may be encountered.

a) The Open part (non-proprietary information) of each APIMF should always be included in its entirety in the application, as an annex to 3.2.S.

b) for an FPP containing more than one API: one complete "3.2.S" section should be provided for one API, followed by other complete "3.2.S" sections for each other API.

c) for an API from multiple manufacturers: one complete "3.2.S" section should be provided for the API from one manufacturer, followed by other complete "3.2.S" sections for each other API manufacturer.

d) for an FPP with multiple strengths (e.g. 10, 50, 100 mg): one complete "3.2.P" section should be provided with the information for the different strengths provided within the subsections. A completed application form should be provided for each FPP strength..

e) for an FPP with multiple container closure systems (e.g. bottles and unit dose blisters): one complete "3.2.P" section should be provided with the information for the different presentations provided within the subsections.

f) for multiple FPPs (e.g. tablets and a parenteral product): a separate dossier is required for each FPP.

g) for an FPP supplied with reconstitution diluent(s), one complete "3.2.P" section should be provided for the FPP, followed by the information on the diluent(s) in a separate part
"3.2.P", as appropriate.

h) for a co-blistered FPP, one complete "3.2.P" section should be provided for each product.

i) In cases where multiple FPP manufacturers are proposed, relevant documents from the respective sites should be provided (e.g. process validation, batch analysis data, specifications, stability data, production documents, etc.)

For more information on when one or separate applications are required, applicants should refer *to the sections below*.

5. CTD MODULES 1-3

Numbering and labelling of folders and files should be done following the CTD format.

MODULE 1

Module 1 should contain all administrative documents (e.g. application forms and certifications), labelling, general correspondence and annexes as needed. Documents should be organised in the

order listed below. Generally, all of the documents in Module 1, other than the annexes, can be provided in a single volume. The annexes to the module should be submitted in separate volumes.

Module 1.0 Cover Letter

Documentation		
1	1.0	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.

Module 1.1 Comprehensive table of contents

Documentation		
1	1.1	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 (section heading according to the CTD format e.g. 3.2.P.4.2). If the full name of the document is too long for the tab identifiers, an alternative name that adequately identifies the document should be substituted.

Page numbers only should not be used in the table of contents to refer to documents, rather; tab identifiers as described above should be used. Page numbers in addition to the tab identifier should be used to facilitate location within documents where relevant.

Module 1.2 Application Form

Documentation		
1	1.2.1	Application Form
2	1.2.2	Annexes to the application form

1.2.1 Application form

Each application for registration of a medicine must be submitted in accordance with the requirements of the Botswana MRA

(i) All forms are to be completed in English,

(ii) Application forms are available from the Botswana Medicines Regulatory Authority website (www.bomra.co.bw) and all completed applications are to be submitted to:

CHIEF EXECUTIVE OFFICER
Botswana Medicines Regulatory Authority Plot 112
Gaborone International Finance Park P/BAG 2
• GABORONE STATION • BOTSWANA

(iii) An application not submitted in the appropriate format, incomplete or illegible will be rejected.

Annex 1.2.2.11 (Quality Information Summary - QIS) should be submitted to BoMRA together with the dossier and all other responses to queries. Updated QIS should also be submitted after every variation approval if applicable.

In addition to the paper dossier, Module 1.2.1 should be submitted electronically on CD or DVD.

An application for registration of a medicine may be made by the prospective holder of the marketing authorization/registration, hereinafter referred to as the applicant.

1.2.2 Annexes to the application form

1.2.2	1.2.2.1	Proof of payment
	1.2.2.2	Letter of authorisation for communication on behalf of the applicant
	1.2.2.3	Electronic copy declaration
	1.2.2.4	Curriculum vitae of the qualified person for pharmacovigilance
	1.2.2.5	API change control
	1.2.2.6	Copy of EMA certificate for a Vaccine Antigen Master File (VAMF)
	1.2.2.7	Copy of EMA certificate for a Plasma Master File (PMF)
	1.2.2.8	Copy of certificate(s) of suitability of the European Pharmacopoeia (CEP)
	1.2.2.9	Copy of confirmation of API prequalification document (CPQ)
	1.2.2.10	Letter of access from the APIMF holder, CEP holder or CPQ holder

1.2.2.1 Proof of payment

The application fees should be paid as required. An application not accompanied by the appropriate fee will not be accepted. A copy of the proof of payment should be included in this section.

1.2.2.2 Letter of authorisation for communication on behalf of the applicant

The suitably qualified person responsible for the compilation of the application must sign the application. This should be an original signature (scanned signature not acceptable). Attach an individualised, person specific letter of authorisation for the signatory, issued by the Person responsible for the overall management and control of the business (CEO).

A letter of Authorisation for the responsible person, if different from the person signing the dossier, to communicate with Botswana MRA should be submitted in this section.

1.2.2.3 Electronic copy declaration

The submissions must comply fully with the Common Technical Document as regards presentation and content of the dossier.

1.2.2.4 Curriculum vitae of the qualified person responsible for pharmacovigilance

Include curriculum vitae of the qualified person responsible for pharmacovigilance.

1.2.2.5 API change control

A formal agreement exists between the manufacturer of the Finished Pharmaceutical Product (FPP) and each manufacturer of the active pharmaceutical ingredient (API), which ensures that information will be communicated between them and to BoMRA before any significant change is made to the site of manufacture, manufacturing procedure or quality control specifications of the API. Except when permitted by BoMRA's Amendments guideline relating to changes to medicines, such changes will not be made to the

API(s) to be used in manufacture of medicines to be distributed in Botswana before written approval is granted by BoMRA. Both parties 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 containing this material in Botswana

A copy of the agreement between API and FPP manufactures should be submitted in this section.

1.2.2.6 Copy of EMA certificate for a Vaccine Antigen Master File (VAMF)

Insert a copy of the European Medicines Agency certificate for a Vaccine Antigen Master File (VAMF) if applicable.

1.2.2.7 Copy of EMA certificate for a Plasma Master File (PMF)

Insert a copy of the European Medicines Agency certificate for a Plasma Master File, if applicable.

1.2.2.8 Copy of certificate(s) of suitability of the *European Pharmacopoeia* (CEP)

Insert a copy of certificate(s) of suitability of the *European Pharmacopoeia* (CEP), if applicable. (Including any annexes).

1.2.2.9 Confirmation of Prequalification (CPQ) of an API

Insert a copy of Confirmation of Prequalification (CPQ) of an API in this section, if applicable.

1.2.2.10 Letter of access from the APIMF holder, CEP holder or CPQ holder

Insert a copy of Letter of access from the APIMF holder, CEP holder or CPQ holder in this section, if applicable.

1.2.2.11 Quality Information Summary QIS

Insert a copy of Quality Information Summary QIS. The updated QIS should also be submitted with responses and variation applications, where applicable. The QIS template should be completed to provide a condensed summary of the key quality information for the application for registration and constitutes part of the submission package. The QIS provides an accurate record of

technical data in the application for registration at the time of registration. The QIS is a condensed version of the QOS- and represents the final agreed upon key API and FPP information from the assessment report (inter alia identification of the manufacturer(s)/site addresses, API/FPP specifications, stability conclusions and relevant commitments).

The QIS template is structured according to the numbering and section headings of the ICH M4Q (CTD-Q) guideline to permit the rapid assembly of the QIS by copying requisite information from the corresponding portions of the QOS-filed with the application for registration. It is acknowledged that the numbering of the sections in the QIS 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 dossier.

The QIS will serve as an official reference document in the course of GMP inspections, variation assessments and renewals.

Module 1.3 Labelling and packaging

Documentation	
1.3.1	Package Insert/SmPC
1.3.2	Patient Information Leaflet
1.3.3	Labels
1.3.4	Braille

Applicants should include the proposed or approved texts of Package Insert (PI) (Module 1.3.1) and Patient Information (PIL) leaflet (Module 1.3.2). Labels complying with specific Botswana MRA requirements should be submitted in Module 1.3.3 (mock-ups, specimens or text).

1.3.1 Package Insert/ SmPC

Modules 1.3.1 should include a copy of the PI - either the proposed PI in the case of a new application, or the currently approved PI in the case of amendments. The PI should

comply with local requirement of Botswana including schedule and registration numbers.

1.3.2 Patient Information Leaflet

Module 1.3.2 should contain a copy of the proposed patient information leaflet (PIL), which should be written in layman's language (Basic English).

1.3.3 Labels

Labels should be prepared as per SADC guideline on product information and labelling.

If the applicant has a specimen or mock-up of the sales presentation of the medicine available at the time of initial application, it should be included in Module 1.3.3.

A mock-up is 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.

A specimen is a sample of the actual printed outer and inner packaging materials and package leaflet. If there are multiple strengths and/or pack sizes, all representative specimens or mock-up should be submitted. If batch number and expiry date are to be printed on the label during packaging, a statement to this effect should accompany the labels.

1.3.4 Braille

For future use.

Module 1.4 Information about the experts

Documentation	
1.4.1	Declaration signed by the expert – Quality
	Information about the Expert – Quality
1.4.2	Declaration signed by the expert – Non-clinical
	Information about the Expert – Non-clinical
	Declaration signed by the expert – Clinical

1.4.3	Information about the Expert – Clinical

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 1.4.
- Brief information on the educational background, training and occupational experience of the experts in Module 1.4.
- In cases concerning well-known active pharmaceutical ingredients, the Council may grant exemption from the submission of sections 1.4.2 and 1.4.3.

References must be provided for any additional claims not supported by the dossier.

Module 1.5 Specific requirements for different types of applications

Documentation		
1.	1.5.1	Application Form
	1.5.2	Annexes to the application form
	1.5.2.1	Tablets/Capsules/Suppositories/Lozenges
	1.5.2.2	Syrups/Liquids/Solutions (non parenterals) /Creams/ointments
	1.5.2.3	Ampoules, Vials and Large Volume Parenterals
	1.5.2.4	Different applicants/proprietary names for the same formula
2.	1.5.3	3Genetically modified organisms (GMO)

1.5.1 Studies and data for generic products

If clinical evidence in support of efficacy is not submitted, studies and data to demonstrate the pharmaceutical and/or biological availability of the product should be included. If in the opinion of the applicant no data are required to substantiate efficacy (e.g. parenteral solutions) the rationale for accepting safety and efficacy, including reference to standard Reference Books, should be clearly stated.

For package insert amendments, refer to the Package Insert Guideline.

1.5.2. Same/Separate Applications

1.5.2.1 Tablets/Capsules/Suppositories/Lozenges

(i) Different pack-sizes of the same strength and formulation will require one application

(ii) Different strengths and/or formulations will require separate applications.

(iii) Co-packed and co-blistered products will require one application.

1.5.2.2 Syrups/Liquids/Solutions (non parenterals)/Creams/ointments

(i) Different container sizes of the same strength and formulation will require one application.

(ii) Same container size of different strengths and/or formulations will require separate applications.

1.5.2.3 Ampoules, Vials and Large Volume Parenterals

(i) Ampoules containing identical solutions of the same strength but of different volumes will require separate applications;

(ii) Ampoules containing solutions of different strengths will require separate applications;

(iii) Ampoules and/or single dose vials containing dry powder, crystals etc, of different mass will require separate applications;

(iv) Ampoules and single dose vials containing the same respective masses of dry powder, crystals etc, will require separate applications;

(v) Ampoules, single dose vials, as well as disposable syringes and cartridges containing identical solutions of the same strength and same volume of liquid will require separate applications.

(vi) Dental cartridges containing fluids of different volumes will require one application;

(vii) Ampoules containing "water for injection", but of different volume will require one application.

(viii) Special ampoules of dry powder and "water for injections" contained in the same unit, but intended for mixing at the time of injection, will require one application.

(ix) Ampoules containing identical solutions of different volumes used only as a diluent in the reconstitution of a preparation for parenteral use, will require separate applications.

(x) Multi-dose vials of the same strength and formulation in different volumes will require separate applications.

(xi) Multi-dose vials and a single dose ampoule of the same formulation will require separate applications.

(xii) Multi-dose vials containing dry powder of different mass and the same formulation, and having the same concentration when reconstituted will require one application.

(xiii) A container of diluent to be used with any preparation in (iii), (iv) or (xii) will require one application provided that the diluent is also fully described in the dossier together with the product.

(xiv) An ampoule of diluent to be used with any biological preparation will require one application;

(xv) Infusion solutions of the same or different volumes and of the same formulation, which are packed in containers of exactly the same type of material, will require separate applications;

(xvi) Infusion solutions of the same or different volumes and of the same formulation, which are packed in containers made of different types of materials, will require separate applications;

(xvii) A preparation, packed in plastic containers and intended also to be marketed in glass containers containing the same volume and the same formulation, will require separate applications.

(xviii) Products with the same strength and formulation but with different colours and/or flavours will require separate applications;

(xix) Applications containing the same active ingredient(s), and where additional indications are sought, where such new indications render the product in a different scheduling status, or different pharmacological classification or have any other restrictions imposed other than the original application, will require separate registration.

1.5.2.4 Different applicants/proprietary names for the same formula

a) Same formula applied under different proprietary names will require separate applications.

b) Same formula from different applicants will require separate applications

Module 1.6 Environmental risk assessment

An application should be accompanied by an environmental risk assessment, evaluating any potential risks of the medicinal product to the environment.

The requirements relate to those risks to the environment arising from use, storage and disposal of medicinal products and not for risks arising from the synthesis or manufacture of medicinal products.

In case of extensive documentation for the environmental risk assessment should always be provided in a separate volume as part of Module 1. In case of a short statement, this can remain in the Module 1 volume(s).

Module 1.7 Good manufacturing practice

Documentation		
1.	1.7.1	Date of last inspection of each site
2.	1.7.2	Inspection reports or equivalent document
3.	1.7.3	Latest GMP certificate API and FPP or a copy of the appropriate licence
	1.7.4	Registration of Responsible Pharmacist or Suitably Qualified Person for local manufacturers
4.	1.7.5	Sample and Documents
	1.7.6	Confirmation of submission of the sample
5.	1.7.7	Certified copy of permit to manufacture specified controlled substances

For all medicines, irrespective of the country of origin, it is expected that key manufacturing and/or processing steps in the production of active ingredients and finished pharmaceutical products are performed in plants of acceptable standards (see WHO GMP Guideline).[1]

[1] www.who.int

1.7.1 Date of last inspection of each site

The applicant should provide a list of manufacturers', packers' and Finished Product Release Controls' (FPRC) names and licence numbers, with a list of the dates of inspection by the Health Authorities of ICH, PIC/S and SADC.

1.7.2 Inspection reports or equivalent document

The applicant should provide copies of inspection reports or equivalent document, not older than three years, from the site conducted by ICH, PIC/S and SADC.

1.7.3 Latest GMP certificate or a copy of the appropriate licence

Include the latest GMP certificate, not older than three years, for manufacturer/s, packer/s and FPRCs or a copy of the appropriate licence.

1.7.4 Registration of Responsible Pharmacist or Suitably Qualified Person for local manufacturers

Proof of current registration of the Responsible Pharmacist or Suitably Qualified Person by the relevant registering Body in the Botswana should be submitted in this section.

1.7.5 Samples and Documents

1.7.5.1 Confirmation of submission of samples: One sample in each of the proposed packaging materials should be submitted for assessment. More samples for testing may be requested as and when necessary/required.

1.7.5.2 CoA of the sample(s)

Include the CoA of the FPP. Ensure that the batch number on the CoA corresponds with the batch number on the sample.

1.7.6 Certified copy of a permit to manufacture specified controlled substances

Include a duly certified permit to manufacture controlled substances, where applicable.

Module 1.8 Details of screening

Documentation	
1.	Screening Checklist

A copy of the completed screening checklist must be included in Module 1.8.
If new document versions are submitted, an updated version of Module 1.2.1 must also be submitted.

Module 1.9 Individual patient data – statement of availability

Documentation	
1.	Declaration concerning availability of individual patient data

Include a statement that raw clinical and pre-clinical data have been removed from the application and that individual patient data are available on request.

Data in respect of each individual patient from each clinical trial are not required to be included in the documentation at the time of application, except in the case of any bioavailability studies where individual patient data (IPD) for plasma concentrations and derived data are required.

Individual patient data may be requested by BoMRA;

- to support a particular study if, during the evaluation, there is any reason to doubt the analysis or conclusions reached;

- if, after registration, the application is selected for auditing of the summary results and conclusions.

Module 1.10 Foreign regulatory status

Documentation		
1.	1.10.1	List of countries in which an application for the same product as being applied for has been submitted, approved, rejected or withdrawn
	1.10.2	WHO type CoPP
	1.10.3	Registration certificates or marketing authorisation
	1.10.4	Foreign prescribing and patient information
	1.10.5	Data set similarities

Applicants are advised that this module should be completed for all applications (including those for multisource products).

1.10.1 List of countries in which an application for the same product as being applied for has been submitted, approved rejected or withdrawn

The applicant should provide, in Module 1.10.1 of the dossier, a list of countries in which an application for the same product as being applied for has been submitted, approved, rejected or withdrawn, including dates of submission (if available).

Reasons for rejection or withdraw should be provided.

If no application has been submitted for registration in the country of origin, include a statement to provide the reason for this decision.

1.10.2 WHO type CoPP

A copy of the WHO-type Certificate of a Pharmaceutical product should be submitted in this section.

1.10.3 Registration certificates or marketing authorisation

In the case of registration in the country of origin, or where a marketing authorisation has been granted by an NMRA of ICH, SADC and others countries that maybe recognised by BoMRA, copies of the registration certificates or marketing authorisation should be supplied in this section.

1.10.4 Foreign prescribing and patient information

In the case of marketing authorisations in country of origin, or where marketing authorisation has been granted by an NMRA of ICH, SADC and others countries that maybe recognised by BoMRA, copies of relevant PI/SmPC and PIL should be submitted in this section.

1.10.5 Data set similarities

Module 1.10.4 should contain a summary of the similarities / differences in the product submitted in ICH, SADC and other countries that maybe recognised by Botswana.

Module 1.11 Bioequivalence trial

Documentation		
1.	1.11.1	Study Title(s) (or brief description giving design, duration, dose and subject population of each study)
	1.11.2	Protocol and study numbers
	1.11.3	Investigational products (test and reference) details in tabulated format, including
		• active ingredient
		• strength
		• dosage form
		• manufacturer
		• batch number
		• expiry or retest date
		• country in which procured
	1.11.4	Confirmation that the test product formulation and manufacturing process is that being applied for
	1.11.5	Proof of procurement of the biostudy reference product (may include cross-reference to Module 5.3.1)
	1.11.6	Name and address of the Research Organisation(s) / Contract Research Organisation(s) where the bioequivalence studies were conducted
	1.11.7.	Sponsor and responsible sponsor representative: name and address, contact details
	1.11.8	Duration of Clinical phase: dates of dosing and last clinical procedure
	1.11.9	Date of final report

Module 1.12 Paediatric development program

Documentation		
1.	1.12	References to paediatric development program

There is a recognised global problem with the availability of paediatric specific formulations and a lack of information from proper investigations of the use of medicines in children. This problem leads to medicines being used outside of their approved indications, and, at times, being reformulated by pharmacists to make them more suitable for use by children. However, the basic precept that children should not be discriminated against by being supplied poorly investigated medicines has been accepted internationally.

The CTD guidelines require that the safety and efficacy in the paediatric population should be routinely analysed in applications for a proposed indication that occurs in children.

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

Module 1.13 Information relating to pharmacovigilance

1.13.1 Pharmacovigilance system
A plan on pharmacovigilance should be submitted in this section

1.13.2 Risk management System
A plan on risk management and or minimisation should be submitted in this section

Module 1.14 Electronic review documents (e.g. product information, BTIF, Botswana–QOS)

Electronic copies of the BTIF, Botswana–QOS, Botswana QIS, and Biowaiver application forms should be submitted.

MODULE 2: COMMON TECHNICAL DOCUMENT SUMMARIES

Module 2 of the CTD dossier contains the summaries and overviews for the quality, non-clinical and clinical sections of the dossier (refer to the European *Notice to Applicants: Medicinal products for human use. Volume 2B: Presentation and format of the dossier CTD* (July 2003).

The Clinical Overview should include a statement regarding Good Clinical Practice (GCP) compliance.

In cases concerning generic, BoMRA may grant exemption from the submission of Non-clinical and Clinical Overviews and Summaries (2.4, 2.5, 2.6 and 2.7). For generics, the following sections should be submitted:
2.1 Table of contents for Module 2
2.2 Introduction
2.3 Quality Overall Summary through form BOMRA/ER/MD/P02/G01/F01

Module 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 reviewer 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 discussed under the CTD-S module), including cross-referencing to volume and page number in other Modules.

All sections and fields in the QOS application for registration 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 the information can be used if they fulfill the same purpose.

Module 1.4.2: Quality information summary (QIS)

The QIS template, *BOMRA/ER/MD/P02/G01/F02*, should be completed to provide a condensed summary of the key quality information for the application for registration and constitutes part of the submission package. The QIS provides an accurate record of technical data in the application for registration at the time of registration. The QIS is a condensed version of the QOS and represents the final agreed upon key API and FPP information from the assessment report (inter alia identification of the manufacturer(s)/site addresses, API/FPP specifications, stability conclusions and relevant commitments).

The QIS template is structured according to the numbering and section headings of the ICH M4Q (CTD-Q) guideline to permit the rapid assembly of the QIS by copying requisite information from the corresponding portions of the QOS filed with the application for registration. It is

acknowledged that the numbering of the sections in the QIS 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 application for registration.

The QIS will serve as an official reference document in the course of GMP inspections, variation assessments and requalification assessments as performed by WHO.

INTRODUCTION

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

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

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

Information from 3.2.S.1 should be included.

2.3.S.2 Manufacture (name, manufacturer)

Information from 3.2.S.2 should include:

- Information on the manufacturer;
- A brief description of the manufacturing process (including, for example, reference to starting materials, critical steps, and reprocessing) and the controls that are intended to result in the routine and consistent production of material(s) of appropriate quality;
- A flow diagram, as provided in 3.2.S.2.2;
- A description of the Source and Starting Material and raw materials of biological origin used in the manufacture of the API, as described in 3.2.S.2.3;
- A discussion of the selection and justification of critical manufacturing steps, process controls, and acceptance criteria. Highlight critical process intermediates, as described in 3.2.S.2.4;

- A description of process validation and/or evaluation, as described in 3.2.S.2.5.

- A brief summary of major manufacturing changes made throughout development and conclusions from the assessment used to evaluate product consistency, as described in 3.2.S.2.6. The QOS should also cross-refer to the non-clinical and clinical studies that used batches affected by these manufacturing changes, as provided in the CTD-S and CTD-E modules of the dossier.

2.3.S.3 Characterization (name, manufacturer)

A summary of the interpretation of evidence of structure and isomerism, as described in 3.2.S.3.1, should be included. When an API is chiral, it should be specified whether specific stereoisomers or a mixture of stereoisomers have been used in the nonclinical and clinical studies, and information should be given as to the stereoisomer of the API that is to be used in the final product intended for marketing.

For NCE/generics: The QOS should summarise the data on potential and actual impurities arising from the synthesis, manufacture and/or degradation, and should summarise the basis for setting the acceptance criteria for individual and total impurities. The QOS should also summarise the impurity levels in batches of the API used in the non-clinical studies, in the clinical trials, and in typical batches manufactured by the proposed commercial process. The QOS should state how the proposed impurity limits are qualified. A tabulated summary of the data provided in 3.2.S.3.2, with graphical representation, where appropriate should be included.

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

A brief summary of the justification of the specification(s), the analytical procedures, and validation should be included. Specification from 3.2.S.4.1 should be provided. A tabulated summary of the batch analyses from 3.2.S.4.4, with graphical representation where appropriate, should be provided.

2.3.S.5 Reference Standards or Materials (name, manufacturer)

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

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

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

2.3.S.7 Stability (name, manufacturer)

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

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

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

2.3.P FINISHED PHARMACEUTICAL PRODUCT (FPP) (NAME, DOSAGE FORM)

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

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

2.3.P.2 Pharmaceutical Development (name, dosage form)

A discussion of the information and data from 3.2.P.2 should be presented.

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

2.3.P.3 Manufacture (name, dosage form)

Information from 3.2.P.3 should include:

- Information on the manufacturer.
- A brief description of the manufacturing process and the controls that are intended to result in the routine and consistent production of product of appropriate quality.
- A flow diagram, as provided under 3.2.P.3.3.
- A brief description of the process validation and/or evaluation, as described in 3.2.P.3.5.

2.3.P.4 Control of Excipients (name, dosage form)

A brief summary on the quality of excipients, as described in 3.2.P.4, should be included.

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

A brief summary of the justification of the specification(s), a summary of the analytical procedures and validation, and characterisation of impurities should be provided. Specification(s) from 3.2.P.5.1 should be provided. A tabulated summary of the batch analyses provided under 3.2.P.5.4, with graphical representation where appropriate should be included.

2.3.P.6 Reference Standards or Materials (name, dosage form)

Information from 3.2.P.6 (tabulated presentation, where appropriate) should be included.

2.3.P.7 Container Closure System (name, dosage form)

A brief description and discussion of the information in 3.2.P.7 should be included.

2.3.P.8 Stability (name, dosage form)

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

A tabulated summary of the stability results from 3.2.P.8.3, with graphical representation where appropriate, should be included. The post-approval stability protocol, as described in 3.2.P.8.2, should be provided.

2.3.A APPENDICES

2.3.A.1 Facilities and Equipment (name, manufacturer)

Not applicable (i.e. not a biotech product)

2.3.A.2 Adventitious Agents Safety Evaluation (name, dosage form and manufacturer)

2.3.A.3 Novel Excipients

2.3.R REGIONAL INFORMATION

A brief description of the information specific for the region, as provided under "3.2.R" should be included, where appropriate.

2.4 Nonclinical Overview

Module 4 of the dossier contains the non-clinical (pharmaco-toxicological) data relevant to the application.

Generally, for well-known active pharmaceutical ingredients (generic medicines), submission of non-clinical overview may be exempted.

2.5 Clinical Overview

Module 5 of the dossier contains the clinical data relevant to the application.

Generally, for well-known active pharmaceutical ingredients (generic medicines), submission of clinical overview may be exempted.

2.6 Nonclinical Written and Tabulated Summaries

Module 4 of the dossier contains the non-clinical (pharmaco-toxicological) data relevant to the application.

Generally, for well-known active pharmaceutical ingredients (generic medicines), submission of non-clinical written and tabulated summaries may be exempted.

2.7 Clinical Summary

Module 5 of the dossier contains the clinical data relevant to the application. Generally, for well-known active pharmaceutical ingredients (generic medicines), submission of clinical summary information may be exempted.

MODULE 3: QUALITY

Module 3 of the dossier contains the chemical, pharmaceutical and biological data relevant to the application.

Refer to the Registration guideline for the current requirements for this module.

Full reports on biopharmaceutics studies, including methodology and validation data for bioavailability studies, should be included in Module 5.3.1.

3.2.R.3 Bioequivalence trial information form (BTIF), *BOMRA/ER/MD/P02/G01/F03*

3.2.R.3.1 A completed BTIF should be submitted both in hard copy and electronic (word format)

3.2.R.3.2 Biowaiver requests in relation to conducting comparative bioavailability study

A completed Biowaiver Application Form, *BOMRA/ER/MD/P02/G01/F04* or BOMRA/ER/MD/P02/G01/F05 (whichever is relevant), should be submitted both in hard copy and electronic (word format).

Requirements for biopharmaceutic studies are described in the following documents:

- EMA Guideline on Investigation of Bioequivalence (also covers additional strength, BCS based biowaivers), EMA Guideline on Bioanalytical Method Validation (Bioanalytical method validation, presentation of biopharmaceutical and bioanalytical data, and pharmacokinetic and clinical evaluation of modified release dosage forms). https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-efficacy-safety-clinical-pharmacology-pharmacokinetics

- ICH M9 on biopharmaceutics classification system based biowaivers https://www.ema.europa.eu/en/ich-m9-biopharmaceutics-classification-system-based-biowaivers

- WHO guidances for organizations performing in vivo bioequivalence studies https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/regulatory-standards/trs966-annex9-invivo-bioequivalence-studies.pdf?sfvrsn=510cfeec_2

3.1. TABLE OF CONTENTS OF MODULE 3

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

3.2. BODY OF DATA

3.2.S DRUG SUBSTANCE (NAME, MANUFACTURER)

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

- Option 1: Confirmation of API Prequalification document (CPQ);
- Option 2: Certificate of suitability of the European Pharmacopoeia (CEP); or
- Option 3: Active pharmaceutical ingredient master file (APIMF) procedure; or
- Option 4: Full details in the dossier.

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

Option 1: Confirmation of API Prequalification document.

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.

- 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 as per guidance in this section.

- 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.

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

- 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.

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

- 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.

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

- 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 lower temperature or humidity to that of the Prequalified API.

Option 2: Certificate of Suitability of the European Pharmacopoeia (CEP)

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

In addition, a written commitment should be included that the applicant will inform Botswana MRA in the event that the CEP is withdrawn. It should also be acknowledged by the applicant

that withdrawal of the CEP would require additional consideration of the API data requirements to support the application. 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.

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

- 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.

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

- 3.2.S.4.2 / 3.2.S.4.3 Analytical procedures and validation – for any methods used by the FPP manufacturer in addition to those in the CEP and Ph.Eur. monograph.

- 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.

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

- 3.2.S.6 Container closure system - specifications including descriptions and identification of primary packaging components. Exception: where the CEP specifies a container closure system and the applicant declares to use the same container closure system.

- 3.2.S.7 Stability - exception: where the CEP specifies a re-test period that is the same as or of longer duration, and storage conditions which are the same or higher temperature and humidity as 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 application.

Option 3: Active pharmaceutical ingredient master file (APIMF) procedure

The API manufacturer may submit full details of the chemistry, manufacturing process, quality controls during manufacturing and process validation for the API as an APIMF.

In such cases, the Open part (non-proprietary information) needs to be included in its entirety in the application as an annex to 3.2.S. In addition, the applicant/FPP manufacturer should complete the following sections in the application and QOS in full according to the guidance provided unless otherwise indicated in the respective sections:

General information S.1.1 through S.1.3

Manufacture S.2

Manufacturer(s) S.2.1

Description of manufacturing process and process controls S.2.2 Controls of critical steps and intermediates S.2.4

Elucidation of structure and other characteristics S.3.1 Impurities S.3.2

Control of the API S.4.1 through S.4.5

Reference standards or materials S.5

Container closure system S.6

Stability S.7.1 through S.7.3

It is the responsibility of the applicant to ensure that the complete APIMF (i.e. both the applicant's Open part and the API manufacturer's Restricted part) is supplied to BoMRA directly by the API manufacturer and that the applicant has access to the relevant information in the APIMF concerning the current manufacture of the API.

A copy of the letter of access should be provided in the Application Module 1.

APIMF holders can use the guidance provided for the option "Full details in the Application" for preparation of the relevant sections of the Open and Restricted parts of their APIMFs. Reference should also be made to the APIMF guideline in WHO Technical Report Series, No. 948, Annex 4.

Option 4: Full details in the Dossier

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 application as outlined in the subsequent sections of this guideline. The QOS should be completed as per Section 3.1 of this guideline.

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

3.2.S.1.1 Nomenclature (name, manufacturer)

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

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

3.2.S.1.2 Structure (name, manufacturer)

NCE & Generics: 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 (name, manufacturer)

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:

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

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

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

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

Polymorphism As recommended in ICH's CTD-Q Questions and answers/location issues document the following refers to where specific data should be located in the application:

- 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

- 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

As recommended in ICH's CTD-Q Questions and Answers/Location Issues document, the 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.

Reference ICH Guidelines: Q6A

3.2.S.2 Manufacture (name, manufacturer)

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

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

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

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

A valid manufacturing authorization should be provided for the production of APIs. A certificate of GMP compliance should also be provided in the application in Module 1.

3.2.S.2.2 Description of Manufacturing Process and Process Controls (name, manufacturer)

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

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

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

As discussed in ICH Q7 and WHO Technical Report Series, No. 957 Annex 2, the point at which the API starting material is introduced into the manufacturing process is the starting point of the application of GMP requirements. The API starting material itself needs to be proposed and its choice justified by the manufacturer and accepted as such by assessors. The API starting material should be proposed taking into account the complexity of the molecule, the proximity of the API starting material to the final API, the availability of the API starting material as a commercial chemical and the quality controls placed upon the API starting material. This justification should be documented in the dossier and be available for review by BoMRA GMP inspectors.

In situations where the API starting material is a complex molecule and only a minimal number of synthetic steps from the final API, a further molecule called the starting material for synthesis should be proposed and its choice justified by the applicant. 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. In the case where the precursor to the API is obtained from fermentation, or is from plant or animal origin, such a molecule can be considered the API starting material regardless of complexity.

A one step synthesis may be accepted in exceptional cases, for example where the API starting material is covered by a CEP, or where the API starting material is an API accepted through the APIMF or API-PQ procedure with the confirmation of a prequalification document, or when the structure of the API is so simple that a one step synthesis can be justified, e.g. ethambutol or ethionamide.

In addition to the detailed description of the manufacturing process as per ICH M4Q, 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, however their use can be justified on presentation of sufficient data demonstrating that recovered solvents meet appropriate standards as outlined in ICH Q7.

Where polymorphic/amorphous forms have been identified, the form resulting from the synthesis should be stated.

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.

It is acceptable to provide information on pilot scale manufacture, provided it is representative of production scale and scale-up is reported immediately to BoMRA according to the requirements of the BoMRA variation guideline.

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

Materials used in the manufacture of the drug substance (e.g., raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials (including biologically-sourced materials, e.g., media components, enzymes) meet standards appropriate for their intended use (including the clearance or control of adventitious agents) should be provided, as appropriate. For biologically sourced materials, this can include information regarding the source, manufacture, and characterization. (Details in 3.2.A.2)

The *API starting material* should be fully characterized and suitable specifications proposed and justified, including at a minimum control for identity, assay, impurity content and any other critical attribute of the material. For each *API starting material*, the name and manufacturing site address of the manufacturer(s) should be indicated. A brief description of the preparation of the *API starting material* should be provided for each manufacturer, including the solvents, catalysts and reagents used. A single set of specifications should be proposed for the starting material that applies to material from all sources. Any future changes to the API starting material manufacturers, mode of preparation or specifications should be notified.

As indicated in section 3.2.S.2 there are occasions where a starting material for synthesis may also need to be defined. In general, the starting material for synthesis described in the application should:

- be a synthetic precursor of one or more synthesis steps prior to the final API intermediate. Acids, bases, salts, esters and similar derivatives of the API, as well as the racemate of a single enantiomer API, are not considered final intermediates;

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

- have well defined specifications that include among others one or more specific identity tests and tests and limits for assay and specified, unspecified and total impurities; and

- be incorporated as a significant structural fragment into the structure of the API.

Copies of the specifications for the materials used in the synthesis, extraction, isolation and purification steps should be provided in the application, 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 application.

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

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

When available, a CEP demonstrating TSE-compliance should be provided. A complete copy of the CEP (including any annexes) should be provided in Module 1.

Reference ICH Guidelines: Q6A

3.2.S.2.4 Controls of Critical Steps and Intermediates (name, manufacturer)

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

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.

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

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

Reference ICH Guidelines: Q6A

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

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

It is expected that the manufacturing processes for all APIs are properly controlled. If the API is prepared as sterile, a complete description should be provided for aseptic processing and/or sterilization methods. The controls used to maintain the sterility of the API during storage and transportation should also be provided. Alternate processes should be justified and described (see guidance in 3.2.S.2.2 for the level of detail expected).

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

NCE & Generics: A description and discussion should be provided of the significant changes made to the manufacturing process and/or manufacturing site of the drug substance used in producing nonclinical, clinical (including comparative bioavailability or biowaiver), scale-up, pilot, and, if available, production scale batches.

Reference should be made to the drug substance data provided in section 3.2.S.4.4.

Reference ICH Guideline: Q3A

3.2.S.3 Characterisation (name, manufacturer)

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

Elucidation of structure

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

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

For APIs that are described in an officially recognized pharmacopoeia, it is generally sufficient to provide copies of the IR spectrum of the API from each of the proposed manufacturer(s) run concomitantly with an officially recognized pharmacopoeial reference standard. See Section .2.S.5 for details on acceptable reference standards or materials.

Isomerism/Stereochemistry

When an API is chiral, it should be specified whether specific stereoisomers or a mixture of stereoisomers have been used in the clinical or comparative biostudies, and information should be given as to the stereoisomer of the API that is to be used in the FPP.

Where the potential for stereoisomerism exists, a discussion should be included of the possible isomers that can result from the manufacturing process and the steps where chirality was introduced. The identicality of the isomeric composition of the API to that of the API in the comparator product should be established. Information on the physical and chemical

properties of the isomeric mixture or single enantiomer should be provided, as appropriate. The API specification should include a test to ensure isomeric identity and purity.

The potential for interconversion of the isomers in the isomeric mixture, or racemisation of the single enantiomer should be discussed.

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

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

Polymorphism

Many APIs can exist in different physical forms in the solid state. Polymorphism is characterized as the ability of an API to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice.

Amorphous solids consist of disordered arrangements of molecules and do not possess a distinguishable crystal lattice. Solvates are crystal forms containing either stoichiometric or nonstoichiometric amounts of a solvent. If the incorporated solvent is water, the solvates are also commonly known as hydrates.

Polymorphic forms of the same chemical compound differ in internal solid-state structure and, therefore, may possess different chemical and physical properties, including packing, thermodynamic, spectroscopic, kinetic, interfacial and mechanical properties. These properties can have a direct impact on API processability, pharmaceutical product manufacturability and product quality/performance, including stability, dissolution and bioavailability. Unexpected appearance or disappearance of a polymorphic form may lead to serious pharmaceutical consequences.

Applicants to the Botswana MRA and API manufacturers are expected to have adequate knowledge about the polymorphism of the APIs used and/or produced. Information on polymorphism can come from the scientific literature, patents, compendia or other references to determine if polymorphism is a concern, e.g. for APIs that are not BCS highly soluble. In

the absence of published data for APIs that are not BSC highly soluble, polymorphic screening will be necessary to determine if the API can exist in more than one crystalline form. Polymorphic screening is generally accomplished via crystallization studies using different solvents and conditions.

There are a number of methods that can be used to characterize the polymorphic forms of an API. Demonstration of a non-equivalent structure by single crystal X-ray diffraction is currently regarded as the definitive evidence of polymorphism. XRPD can also be used to provide unequivocal proof of polymorphism. Other methods, including microscopy, thermal analysis (e.g. DSC, thermal gravimetric analysis and hot-stage microscopy) and spectroscopy (e.g. IR, Raman, solid-state nuclear magnetic resonance [ssNMR]) are 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.

Decision tree 4(1) of ICH Q6A can be used where screening is necessary and 4(2) can be used to investigate if different polymorphic forms have different properties that may affect performance, bioavailability and stability of the FPP and to decide whether a preferred polymorph should be monitored at release and on storage of the API. Where there is a preferred polymorph, acceptance criteria should be incorporated into the API specification to ensure polymorphic equivalence of the commercial material and that of the API batches used in the comparative bioavailability or biowaiver studies. The polymorphic characterization of the API batches used in clinical or comparative bioavailability or biowaiver studies by the above-mentioned methods should be provided. The method used to control polymorphic form should be demonstrated to be specific for the preferred form.

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

- specifications for the solvent-free API in 3.2.S.2.4, if that compound is a synthetic precursor;

- specifications for the solvated API including appropriate limits on the weight ratio of API to solvent (with data to support the proposed limits);

- a description of the method used to prepare the solvate in 3.2.S.2.2.

Particle size distribution

For APIs that are not BCS highly soluble contained in solid FPPs, or liquid FPPs containing undissolved API, the particle size distribution of the material can have an effect on the in vitro and/or in vivo behaviour of the FPP. Particle size distribution can also be important in dosage form performance (e.g. delivery of inhalation products), achieving uniformity of content in low-dose tablets (e.g. 2 mg or less), desired smoothness in ophthalmic preparations and stability of suspensions.

If particle size distribution is an important parameter (e.g. as in the above cases), results from an investigation of several batches of the API should be provided, including characterization of the batch(es) used in the comparative bioavailability or biowaiver studies. API specifications should include controls on the particle size distribution to ensure consistency with the material in the batch(es) used in the comparative bioavailability and biowaiver studies (e.g. limits for d10, d50 and d90). The criteria should be established statistically based on the standard deviation of the test results from the previously mentioned studies. The following is provided for illustrative purposes as possible acceptance criteria for particle size distribution limits:

- d10 Not more than (NMT) 10% of total volume less than X µm

- d50 XX µm - XXX µm

- d90 Not less than (NLT) 90% of total volume less than XXXX µm.

- Other controls on particle size distribution can be considered acceptable, if scientifically justified.

Reference ICH Guideline: Q6A

3.2.S.3.2 Impurities (name, manufacturer)

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.

Additional information to provide further guidance on some of the elements discussed in the ICH guidelines is outlined below.

Regardless of whether a pharmacopoeial standard is claimed, a 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.

The tables in the QOS template should be used to summarize the information on the API-related and process-related impurities. In the QOS, the term origin refers to how and where the impurity was introduced (e.g. "Synthetic intermediate from Step 4 of the synthesis", "Potential by-product due to rearrangement from Step 6 of the synthesis"). It should also be indicated if the impurity is a metabolite of the API.

The ICH thresholds for reporting, identification (used to set the limit for individual unknown impurities) and qualification are determined on the basis of potential exposure to the impurity, e.g. by the maximum daily dose (MDD) of the API. For APIs available in multiple dosage forms and strengths having different MDD values, it is imperative that the thresholds and corresponding controls for each of the presentations be considered to ensure that the risks posed by impurities have been addressed. This is normally achieved by using the highest potential daily MDD, rather than the maintenance dose. For parenteral products, the maximum hourly dose of the API should also be included.

It is acknowledged that APIs of semi-synthetic origin do not fall within the scope of the ICH impurity guidelines. However, depending on the nature of the API and the extent of the chemical modification steps, the principles on the control of impurities (e.g. reporting, identification and qualification) could also be extended to APIs of semi-synthetic origin. As an illustrative example, an API whose precursor molecule was derived from a fermentation

process, or a natural product of plant or animal origin that has subsequently undergone several chemical modification reactions generally would fall within this scope, whereas an API whose sole chemical step was the formation of a salt from a fermentation product generally would not fall within this scope. It is understood that there is some latitude for these types of APIs.

Identification of impurities

It is recognized by the pharmacopoeias that APIs can be obtained from various sources and thus can contain impurities not considered during the development of the monograph. Furthermore, a change in the production or source may give rise to additional impurities that are not adequately controlled by the official compendial monograph. As a result, each application is assessed independently to consider the potential impurities that may arise from the proposed route(s) of synthesis. For these reasons, the ICH limits for unspecified impurities (e.g. NMT 0.10% or 1.0 mg per day intake (whichever is lower) for APIs having a maximum daily dose ≤2 g/day) are generally recommended, rather than the general limits for unspecified impurities that may appear in the official compendial monograph that could potentially be higher than the applicable ICH limit.

Qualification of impurities

The ICH impurity guidelines should be consulted for options on the qualification of impurities. The limit specified for an identified impurity in an officially recognized pharmacopoeia is generally considered to be qualified. The following is an additional option for qualification of impurities in existing APIs:

> The limit for an impurity present in an existing API can be accepted by comparing the impurity results found in the existing API with those observed in an innovator product using the same validated, stability-indicating analytical procedure (e.g. comparative HPLC studies). If samples of the innovator product are not available, the impurity profile may also be compared to a different prequalified FPP with the same route of administration and similar characteristics (e.g. tablet versus capsule). It is recommended that the studies be conducted on comparable samples (e.g. age of samples) to obtain a meaningful comparison of the impurity profiles.

Levels of impurities generated from studies under accelerated or stressed storage conditions of the innovator or prequalified FPP are not considered acceptable/qualified.

A specified impurity present in the existing API is considered qualified if the amount of the impurity in the existing API reflects the levels observed in the innovator or prequalified FPP.

Basis for setting the acceptance criteria

The basis for setting the acceptance criteria for the impurities should be provided. This is established by considering the identification and qualification thresholds for API-related impurities (e.g. starting materials, by-products, intermediates, chiral impurities or degradation products) and the concentration limits for process-related impurities (e.g. residual solvents) as per the applicable ICH guidelines (e.g. Q3A, Q3C).

The qualified level should be considered as the maximum allowable limit. However, limits, which are considerably wider than the actual manufacturing process capability, are generally discouraged. For this reason, the acceptance criteria are also set taking into consideration the actual levels of impurities found in several batches of the API from each manufacturer, including the levels found in the batches used for the comparative bioavailability or biowaiver studies. When reporting the results of quantitative tests, the actual numerical results should be provided rather than vague statements such as "within limits" or "conforms". In the cases where a large number of batches have been tested it is acceptable to summarize the results of the total number of batches tested with a range of analytical results.

If there are identified impurities specified in an official compendial monograph that are not controlled by the proposed routine in-house analytical procedure, a justification for their exclusion from routine analyses should be provided (e.g. "Impurities D, E and F listed in the Ph.Int. monograph are not potential impurities from the proposed route of synthesis used by manufacturer X"). If acceptable justification cannot be provided it should be demonstrated that the routine in-house method is capable of separating and detecting the impurities specified in the official compendial monograph at an acceptable level (e.g. 0.10%). If such a demonstration cannot be performed, a one-time study should be conducted applying the pharmacopoeial method to several recent batches to demonstrate the absence of the pharmacopoeial listed impurities.

ICH class II solvent(s) used prior to the last step of the manufacturing process may be exempted from routine control in API specifications if suitable justification is provided. Submission of results demonstrating less than 10% of the ICH Q3C limit (option I) of the solvent(s) in three consecutive production-scale batches or six consecutive pilot-scale batches of the API or a suitable intermediate would be considered acceptable justification. The last step solvents used in the process should always be routinely controlled in the final API.

For guidance on acceptable residual solvent limits, refer to ICH Q3C. The limit for residues of triethylamine (TEA) is either 320 ppm on the basis of ICH Q3C option I or 3.2 mg/day on the basis of permitted daily exposure (PDE).

The absence of known established highly toxic impurities (genotoxic) used in the process or formed as a by-product should be discussed and suitable limits should be proposed. The limits should be justified by appropriate reference to available guidances (e.g. EMEA/CHMP/QWP/251344/2006 or USFDA Guidance for Industry: Genotoxic and carcinogenic impurities in drug substances and products, recommended approaches, December 2008); to make it more generic, when making a reference we should look for the most recent version of the guideline to verify if there is an ICH guideline or by providing experimental safety data or published data in peer-reviewed journals.

Residues of metal catalysts used in the manufacturing process and determined to be present in batches of API are to be controlled in specifications. This requirement does not apply to metals that are deliberate components of the pharmaceutical substance (such as a counter ion of a salt) or metals that are used as a pharmaceutical excipient in the FPP (e.g. an iron oxide pigment). The ICH Q3D guideline on the specification limits for residues of metal catalysts or metal reagents or any equivalent approaches can be used to address this issue. The requirement normally does not apply to extraneous metal contaminants that are more appropriately addressed by GMP, GDP or any other relevant quality provision such as the heavy metal test in monographs of recognized pharmacopoeias that cover metal contamination originating from manufacturing equipment and the environment.

Reference ICH Guidelines: Q3A, Q3C, and Q6A

3.2.S.4 Control of Drug Substance (name, manufacturer)

3.2.S.4.1 Specification (name, manufacturer)

As defined in ICH's Q6A guideline, a specification is:

> *"a list of tests, references to analytical procedures and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which an API or FPP should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the API and / or FPP, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities."*

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 application, 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).

- The standard declared by the applicant could be an officially recognized compendial standard (e.g. Ph.Int., Ph.Eur., BP, USP, JP) or any other pharmacopoeias recognized by specific countries… or in-house (manufacturer's) standard.

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

  For the analytical procedures, the type should indicate the kind of analytical procedure used (e.g. visual, IR, UV, HPLC, laser diffraction), the source refers to the origin of the analytical procedure (e.g. Ph.Int., Ph.Eur., BP, USP, JP, 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.

The ICH Q6A guideline outlines recommendations for a number of universal and specific tests and criteria for APIs.

Reference ICH Guidelines: Q6A

3.2.S.4.2 Analytical Procedures (name, manufacturer)

Copies of the in-house analytical procedures used to generate testing results provided in the application, 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.

Tables for summarizing a number of the different analytical procedures and validation information (e.g. HPLC assay/impurity methods, GC methods) can be found in the 2.3.R Regional information section of the QOS (i.e. 2.3.R.2). These tables should be used to summarize the in-house analytical procedures of the FPP manufacturer for determination of the residual solvents, assay and purity of the API, in section 2.3.S.4.2 of the QOS. Other methods used to generate assay and purity data in the application can be summarized in 2.3.S.4.4 (c) or 2.3.S.7.3 (b) of the QOS. Officially recognized compendial methods need not be summarized unless modifications have been made.

Although HPLC is normally considered the method of choice for determining API-related impurities, other chromatographic methods such as GC and TLC can also be used, if appropriately validated. For determination of related substances, reference standards should normally be available for each of the identified impurities; particularly those known to be toxic and the concentration of the impurities should be quantitated against their own reference standards. Impurity standards may be obtained from pharmacopoeias (individual impurities or resolution mixtures), from commercial sources or prepared in-house. It is considered acceptable to use the API as an external standard to estimate the levels of impurities, provided

the response factors of those impurities are sufficiently close to that of the API, i.e. between 80 and 120%. In cases where the response factor is outside this range, it may still be acceptable to use the API, provided a correction factor is applied. Data to support calculation of the correction factor should be provided for an in-house method. Unspecified impurities may be quantitated using a solution of the API as the reference standard at a concentration corresponding to the limit established for individual unspecified impurities (e.g. 0.10%). The test for related substances in the Ph. Int. monograph for lamivudine serves as a typical example.

The system suitability tests (SSTs) represent an integral part of the method and are used to ensure the adequate performance of the chosen chromatographic system. As a minimum, HPLC and GC purity methods should include SSTs for resolution and repeatability. For HPLC methods to control API-related impurities, this is typically done using a solution of the API with a concentration corresponding to the limit for unspecified impurities. Resolution of the two closest eluting peaks is generally recommended. However, the choice of alternate peaks can be used if justified (e.g. choice of a toxic impurity). In accordance with the Ph.Int. section on Methods of Analysis, the repeatability test should include an acceptable number of replicate injections. HPLC assay methods should include SSTs for repeatability and in addition either peak asymmetry, theoretical plates or resolution. For TLC methods, the SSTs should verify the ability of the system to separate and detect the analyte(s) (e.g. by applying a spot corresponding to the API at a concentration corresponding to the limit of unspecified impurities).

Reference ICH Guidelines: Q2A, WHO Technical Report Series, No. 943, Annex 3

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

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

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

Tables for summarizing a number of the different analytical procedures and validation information (e.g. HPLC assay/impurity methods, GC methods) can be found in the 2.3.R

Regional information section of the QOS (i.e. 2.3.R.2). These 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 application can be summarized in 2.3.S.4.4 (c) or 2.3.S.7.3 (b) of the QOS.

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 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.

3.2.S.4.4 Batch Analyses (name, manufacturer)

The information provided should include batch number, batch size, date and production site of relevant API batches used in comparative bioavailability or biowaiver studies, preclinical and clinical data (if relevant), stability, pilot, scale-up and, if available, production-scale batches. This data is used to establish the specifications and evaluate consistency in API quality.

Analytical results should be provided from at least two batches of at least pilot scale from each proposed manufacturing site of the API and should include the batch(es) used in the comparative bioavailability or biowaiver studies. A pilot-scale batch should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

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. The FPP manufacturer's test results should be summarized in the QOS.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as "all tests meet specifications". 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).

Reference ICH Guidelines: Q3A, Q3C, and Q6A

3.2.S.4.5 Justification of Specification (name, manufacturer

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 application (e.g. impurities, particle size distribution) and does not need to be repeated here, although a cross-reference to their location should be provided

Reference ICH Guidelines: Q3A, Q3C, Q6A, officially recognized pharmacopeia

3.2.S.5 Reference Standards or Materials (name, manufacturer)

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

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

A suitable primary reference standard should be obtained from an officially recognized pharmacopoeial source (e.g. Ph.Int., Ph.Eur., BP, USP, JP) where one exists and the lot number

should be provided. Where a pharmacopoeial standard is claimed for the API and/or the FPP, the primary reference standard should be obtained from that pharmacopoeia when available. 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).

Reference standards should normally be established for specified impurities. Refer to 3.2.S.4.2 for additional guidance.

Reference ICH Guidelines: Q6A, WHO Technical Report Series, No. 943, Annex

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

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

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

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).

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

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

The WHO Guidelines on packaging for pharmaceutical products (WHO Technical Report Series, No. 902, Annex 9, 2002) and the officially recognized pharmacopoeias should be consulted for recommendations on the packaging information for APIs.

3.2.S.7 Stability (name, manufacturer)

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

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 Botswana guideline *Stability testing of active pharmaceutical ingredients and finished pharmaceutical products* should be consulted for recommendations on the core stability data package required for the prequalification of APIs and FPPs.

As outlined in the Botswana stability guideline, 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 tables in the QOS- template should be used to summarize the results from the stability studies and related information (e.g. conditions, testing parameters, conclusions, commitments).

Stress testing

As outlined in the ICH Q1A guidance document, 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. The nature of the stress testing will depend on the individual API and the type of FPP involved.

Stress testing may be carried out on a single batch of the API. For examples of typical stress conditions refer to Botswana Stability Guideline, as well as, "A typical set of studies of the degradation paths of an active pharmaceutical ingredient" in Botswana Stability Guideline.

The objective of stress testing is not to completely degrade the API, but to cause degradation to occur to a small extent, typically 10-30% loss of active by assay when compared with non-degraded API. This target is chosen so that some degradation occurs, but not enough to generate secondary products. For this reason, the conditions and duration may need to be varied when the API is especially susceptible to a particular stress factor. In the total absence of degradation products after 10 days, the API is considered stable under the particular stress condition.

The tables in the QOS template should be used to summarize the results of the stress testing and should include the treatment conditions (e.g. temperatures, relative humidities, concentrations of solutions, durations) and the observations for the various test parameters (e.g. assay, degradation products). The discussion of results should highlight whether mass balance was observed.

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.

When available, it is acceptable to provide the relevant data published in the scientific literature (inter alia WHOPARs, EPARs) to support the identified degradation products and pathways.

Accelerated and long-term 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 is either 25°C±2°C/60%±5%RH, 30°C±2°C/65%±5%RH or 30°C±2°C/75%±5%RH. Studies covering the proposed re-test period at the above mentioned long-term storage conditions would provide better assurance of the stability of APIs at the conditions of the supply chain corresponding to the Botswana's environment. Alternative conditions should be supported with appropriate evidence, which may include literature references or in-house studies, demonstrating that storage at 30°C is inappropriate for the API.

For APIs intended for storage in a refrigerator and those intended for storage in a freezer refer to the ICH Q1A guideline. APIs intended for storage below -20°C should be treated on a case-by-case basis.

To establish the re-test period, data should be provided on not less than three batches of at least pilot scale. The batches should be manufactured by the same synthesis route as production batches and using a method of manufacture and procedure that simulates the final process to be used for production batches. The stability-testing programme should be summarized and the results of stability testing should be summarized in the dossier and in the tables in the QOS.

The information on the stability studies should include details such as storage conditions, batch number, batch size, container closure system and completed (and proposed) test

intervals. The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as "all tests meet specifications". Ranges of analytical results where relevant and any trends that were observed should be included. For quantitative tests (e.g. individual and total degradation product tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements such as "within limits" or "conforms". Where different from the methods described in S.4.2, descriptions and validation of the methodology used in stability studies should be provided.

The minimum data required at the time of submitting the dossier (in the general case)

Storage temperature (°C)	Relative humidity (%)	Minimum time period (months)
Accelerated 40±2	75±5	6
Intermediate *	*	*
Long term 30±2	65±5 or 75±5	12

Where long-term conditions are 30°C±2°C/65%± 5%RH or 30°C ± 2°C/75%±5%RH, there is no intermediate condition.

Refer to Botswana Stability Guideline for further information regarding the storage conditions, container closure system, test specifications and testing frequency.

Proposed storage statement and re-test period

A storage statement should be established for display on the label based on the stability evaluation of the API. The WHO stability guideline includes a number of recommended storage statements that should be used, when supported by the stability studies.

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

After this re-test period, a batch of API destined for use in the manufacture of an FPP could be re-tested and then, if in compliance with the specification, could be used immediately (e.g. within 30 days). If re-tested and found compliant, the batch does not receive an additional period corresponding to the time established for the re-test period. However, an API batch

can be re-tested multiple times and a different portion of the batch used after each re-test, as long as it continues to comply with the specification. For APIs known to be labile (e.g. certain antibiotics), it is more appropriate to establish a shelf life rather than a re-test period (reference: ICH Q1A).

Limited extrapolation of the real time data from the long-term storage condition beyond the observed range to extend the re-test period can be undertaken at the time of assessment of the application, if justified. Applicants should consult the ICH Q1E guideline for further details on the evaluation and extrapolation of results from stability data (e.g. if significant change was not observed within 6 months at accelerated condition and the data show little or no variability, the proposed re-test period could be up to two times the period covered by the long-term data, but should not exceed the long-term data by 12 months).

Reference ICH Guidelines: Q1A, and Q1B

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

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

Primary stability study commitment

When available long-term stability data on primary batches do not cover the proposed re-test period granted at the time of assessment of the application, a commitment should be made to continue the stability studies in order to firmly establish the re-test period. A written commitment (signed and dated) to continue long-term testing over the re-test period should be included in the dossier when relevant.

Commitment stability studies

The long-term stability studies for the commitment batches should be conducted through the proposed re-test period on at least three production batches. Where stability data was not provided for three production batches, a written commitment (signed and dated) should be included in the dossier.

The stability protocol for the commitment batches should be provided and should include, but not be limited to, the following parameters:

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

Ongoing stability studies

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

At least one production batch per year of API (unless none is produced during that year) should be added to the stability-monitoring programme and tested at least annually to confirm the stability. In certain situations, additional batches should be included. A written commitment(signed and dated) for ongoing stability studies should be included in the dossier.

Refer to Botswana Stability Guideline for further information on ongoing stability studies.

Any differences in the stability protocols used for the primary batches and those proposed for the commitment batches or ongoing batches should be scientifically justified.

Reference ICH Guidelines: Q1A, Q1B, Q1D, and Q1E.

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

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

The actual stability results used to support the proposed re-test period should be included in the dossier. For quantitative tests (e.g. individual and total degradation product tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements such as "within limits" or "conforms". Reference ICH Guidelines: Q1A, Q1B, Q1D, Q1E, and Q2.

3.2.P FINISHED PHARMACEUTICAL PRODUCT (FPP) (NAME, DOSAGE FORM)

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

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

- 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, e.g.

    - "The proposed XYZ 50mg Tablets are available as white, oval, film-coated tablets, debossed with "50" on one side and a break-line on the other side.

    - The proposed XYZ 100mg Tablets are available as yellow, round, film-coated tablets, debossed with "100" on one side and plain on the other side."

- Composition, i.e., list of all components of the dosage form, and their amount on a per-unit basis (including overages, if any) the function of the components, and a reference to their quality standards (e.g., compendial monographs or manufacturer's specifications)

- 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 percentage basis, including a statement of the total weight or measure of the dosage unit. The individual components for mixtures prepared in-house (e.g. coatings) should be included in the tables, where applicable.

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

- The qualitative composition, including solvents, should be provided for all proprietary components or blends (e.g. capsule shells, colouring blends, imprinting inks). This information (excluding the solvents) is to be listed in the product information (e.g. summary of product characteristics, labelling, package leaflet).

- Description of accompanying reconstitution diluents (s); and

  - For FPPs supplied with reconstitution diluent(s) that are commercially available or have been assessed and considered acceptable in connection with another dossier with the MRA, a brief description of the reconstitution diluents(s) should be provided.

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

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

- The container closure used for the FPP (and accompanying reconstitution diluent, if applicable) should be briefly described, with further details provided under 3.2.P.7 Container closure system, e.g.

- "The product is available in HDPE bottles with polypropylene caps (in sizes of 100"s, 500"s and 1000"s) and in PVC/Aluminum foil unit dose blisters (in packages of 100"s (cards of 5x2, 10 cards per package)."

Reference ICH Guidelines: Q6A

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

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

Pharmaceutical development information should include, at a minimum:

- 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;

- 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;

- 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;

- 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 lifecycle of the product (ref: ICH Q8).

For a discussion of additional pharmaceutical development issues specific to the development of FDCs, reference should be made to WHO Technical Report Series, No. 929, Annex 5, Section 6.3.2.

Reference ICH Guidelines: Q6A , Q8, Q9, Q10, WHO Technical Report Series, No. 929, Annex 5,

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

3.2.P.2.1.1 Drug Substance (name, dosage form)

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

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

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

Guidance on compatibility studies is provided in Appendix 3 of the WHO Guidelines for registration of fixed-dose combination medicinal products (WHO Technical Report Series, No. 929, Annex 5, 2005). In addition to visual examination, chromatographic results (assay, purity) are required to demonstrate API-API and API- excipient compatibility. In general, API-excipient compatibility is not required to be established for specific excipients when evidence is provided (e.g. SmPC or product leaflet) that the excipients are present in the comparator product.

3.2.P.2.1.2 Excipients (name, dosage form)

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

When choosing excipients, those with a compendial monograph are generally preferred and may be required in certain jurisdictions. Other resources are available for information on acceptable excipients and their concentrations, such as the US-FDA IIG list and the Handbook of Pharmaceutical Excipients. Use of excipients in concentrations outside of established ranges is discouraged and generally requires justification. In addition, available guidelines should be referenced which address particular excipients to be avoided, for example azo colorants as listed in the EMA Guideline CPMP/463/00, and the Colorcon Regulatory Information Sheet on Azo and non-azo colorants. Other guidance such as the WHO Guideline on development of Paediatric Medicines' may provide useful general guidance in this regard.

Ranges or alternates for excipients are normally not accepted, unless supported by appropriate process validation data. Where relevant, compatibility study results (e.g. compatibility of a primary or secondary amine API with lactose) should be included to justify the choice of excipients. Specific details should be provided where necessary (e.g. use of potato or corn starch).

Where antioxidants are included in the formulation, the effectiveness of the proposed concentration of the antioxidant should be justified and verified by appropriate studies.

Antimicrobial preservatives are discussed in 3.2.P.2.5.

3.2.P.2.2 Drug Product (name, dosage form)

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

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

Botswana defines an established generic product as one that has been marketed by the applicant or manufacturer associated with the dossier for at least five years and for which at least 10 production batches were produced over the previous year, or, if less than 10 batches were produced in the previous year, not less than 25 batches were produced in the previous three years. For products that meet the criteria of an established generic product, all sections of P.2.2.1 of the dossier and QOS should be completed with the exception of P.2.2.1 (a). In addition, a product quality review should be provided as outlined in Appendix 2.

The requirements for bioequivalence studies should be taken into consideration for example when formulating multiple strengths and/or when the product(s) may be eligible for a biowaiver. Botswana BA/BE guideline should be consulted. For generic products, the Applicant should document how a representative batch of the reference product with regards to dissolution and assay content has been selected. It is advisable to investigate more than one single batch of the reference product when selecting reference product batch for the bioequivalence study.

Product scoring may be recommended or required if specified in the description of an innovator or other acceptable reference product or when division into fractional doses may be necessary according to approved posology.

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 dossier 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 for split portions containing less than

5 mg or less than 5% of the weight of the dosage unit portion, or mass uniformity for other situations) should be performed on each split portion from a minimum of 10 randomly selected whole tablets. As an illustrative example, the number of units (i.e. the splits) would be 10 halves for bisected tablets (one half of each tablet is retained for the test) or 10 quarters for quadrisected tablets (one quarter of each tablet is retained for the test). At least one batch of each strength should be tested. Ideally, the study should cover a range of the hardness values. The splitting of the tablets should be performed in a manner that would be representative of that used by the consumer (e.g. manually split by hand). The uniformity test on split portions can be demonstrated on a one-time basis and does not need to be added to the FPP specification(s). The tablet description in the FPP specification and in the product information (e.g. summary of product characteristics, labelling, package leaflet) should reflect the presence of a score.

If splitting of a tablet is intended for a paediatric dose, a demonstration of content uniformity of tablet fragments may be required.

Where relevant, labelling should state that the score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

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. Use of a single point test or a dissolution range should be justified based on the solubility and/or biopharmaceutical classification of the API.

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

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

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

Recommendations for conducting and assessing comparative dissolution profiles can be found in Appendix 1.

3.2.P.2.2.2 Overages (name, dosage form)

Any overages in the formulation(s) described in 3.2.P.1 should be justified.

Justification of an overage to compensate for loss during manufacture should be provided, including the step(s) where the loss occurs, the reasons for the loss and batch analysis release data (assay results).

Overages for the sole purpose of extending the shelf life of the FPP are not acceptable.

3.2.P.2.2.3 Physicochemical and Biological Properties (name, dosage form)

Parameters relevant to the performance of the drug product, such as pH, ionic strength, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency, and/or immunological activity, should be addressed. This list is not exhaustive; other additional properties specific to the API need to be discussed.

The discussion of the above properties should be in relation to the API lot used to manufacture the Clinical batch.

3.2.P.2.3 Manufacturing Process Development (name, dosage form)

The selection and optimization of the manufacturing process described in 3.2.P.3.3, in particular its critical aspects, should be explained. Where relevant, the method of 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 pivotal clinical batches and the process described in 3.2.P.3.3 that can influence the performance of the product should be discussed.

For products that meet the criteria of an established multisource product, in order to fulfill the requirements of section P.2.3, section P.2.3 (b) of the dossier and QOS should be completed and a product quality review should be submitted as outlined in Appendix 2. The guidance that follows applies to all other products, for which section P.2.3 should be completed in its entirety.

The rationale for choosing the particular pharmaceutical product (e.g. dosage form, delivery system) should be provided. The scientific rationale for the choice of the manufacturing, filling and packaging processes that can influence FPP quality and performance should be explained (e.g. wet granulation using high shear granulator). API stress study results may be included in the rationale. Any developmental work undertaken to protect the FPP from deterioration should also be included (e.g. protection from light or moisture).

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 (ref: ICH Q8).

3.2.P.2.4 Container Closure System (name, dosage form)

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

Testing requirements to verify the suitability of the container closure system contact material(s) depend on the dosage form and route of administration. The pharmacopoeias provide standards that are required for packaging materials, including for example the following:

Glass containers:	USP <660> Ph.Eur 3.2.1
Plastic containers:	Ph.Eur 3.2.2, 3.2.2.1 USP <661>
Rubber/Elastomeric closures:	USP <381> Ph.Eur 3.2.9

The following table outlines the general recommendations for the various dosage forms for one-time studies to establish the suitability of the container closure system contact materials.

	Solid Oral Products	Oral Liquid and Topical products	Sterile Products (Including Ophthalmics)
Description of any additional treatments*	X	X	X (sterilization and depyrogenation of the components)
Extraction studies	---	X	X
Interaction studies (Migration/Sorption)	---	X	X
Moisture permeability	X (uptake)	X (usually loss)	X (usually loss)
Light transmission	X**	X	X

*e.g. coating of tubes, siliconization of rubber stoppers, sulphur treatment of ampoules/vials

X = information should be submitted

--- = Information does not need to be submitted

**Not required if product has been shown to be photostable

For solid oral dosage forms and solid APIs, compliance with regulations on food-contact plastic materials, (for example (EU) No. 10/2011) can be considered acceptable.

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.

A device is required to be included with the container closure system for oral liquids or solids (e.g. solutions, emulsions, suspensions and powders/granules for such), any time the package provides for multiple doses.

In accordance with the Ph.Int. general chapter Liquid Preparations for Oral Use:

> *"Each dose from a multidose container is administered by means of a device suitable for measuring the prescribed volume. The device is usually a spoon or a cup for volumes of 5 ml or multiples thereof, or an oral syringe for other volumes or, for oral drops, a suitable dropper."*

For a device accompanying a multidose container, the results of a study should be provided demonstrating the reproducibility of the device (e.g. consistent delivery of the intended volume), generally at the lowest intended dose.

A sample of the device should be provided with Module 1.

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

Where appropriate, the microbiological attributes of the dosage form should be discussed, including, for example, the rationale for not performing microbial limits testing for non-sterile products and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed. Where an antimicrobial preservative is included in the formulation, the amount used should be justified by submission of results of the product formulated with different concentrations of the preservative(s) to demonstrate the least necessary but still effective concentration. The effectiveness of the agent should be justified and verified by appropriate studies (e.g. USP or Ph.Eur. general chapters on antimicrobial preservatives) using a batch of the FPP. If the lower limit for the proposed acceptance criterion for the assay of the preservative is less than 90.0%, the effectiveness of

the agent should be established with a batch of the FPP containing a concentration of the antimicrobial preservative corresponding to the lower proposed acceptance criteria.

As outlined in the Botswana stability guideline a single primary stability batch of the FPP should be tested for effectiveness of the antimicrobial preservative (in addition to preservative content) at the proposed shelf life for verification purposes, regardless of whether there is a difference between the release and shelf life acceptance criteria for preservative content

3.2.P.2.6 Compatibility (name, dosage form)

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

3.2.P.3 Manufacture (name, dosage form)

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

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

The facilities involved in the manufacturing, packaging, labelling and testing should be listed. If certain companies are responsible only for specific steps (e.g. manufacturing of an intermediate), this should be clearly indicated. (Ref: WHO good distribution practices for pharmaceutical products, WHO Technical Report Series, No. 957, Annex 5.)

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.

For a mixture of an API with an excipient, the blending of the API with the excipient is considered to be the first step in the manufacture of the final product and therefore the mixture does not fall under the definition of an API. The only exceptions are in the cases where the API cannot exist on its own. Similarly, for a mixture of APIs, the blending of the APIs is considered to be the first step in the manufacture of the final product. Sites for such manufacturing steps should be included in this section.

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 (Module 1, 1.2.2).

For each site where the major production step(s) are carried out attach a WHO-type certificate of GMP issued by PICS, WHO, ICH, SADC countries and the competent authority in terms of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (Module 1, 1.2.2).

Justification for any differences to the product in the country or countries issuing the WHO- type certificate(s)

When there are differences between the product for which this application is submitted and that marketed in the country/countries which provided the WHO-type certificate(s), provide data to support the applicability of the certificate(s) despite the differences. Depending on the case, it may be necessary to provide validation data for differences in site of manufacture, specifications, formulation, etc. Note that only minor differences are likely to be acceptable. Differences in container labelling need not normally be justified.

Regulatory situation in other countries

The countries should be listed in which this product has been granted a marketing authorization, this product has been withdrawn from the market and/or this application for marketing has been rejected, deferred or withdrawn (Module 1, 1.2.2).

Reference documents: WHO Technical Report Series, No. 961, Annex 3 and No. 957, Annex 5.

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

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

The tables in the QOS 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 components 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 components should be declared by their proper or common names, quality standards (e.g. Ph.Int., Ph.Eur., BP, USP, JP, 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 (name, dosage form)

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

A narrative description of the manufacturing process, including packaging, that represents the sequence of steps undertaken and the scale of production should also be provided. Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater level of detail. Equipment should, at least, be identified by type (e.g., tumble blender, in-line homogeniser) 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 each stage of manufacturing should be stated. The holding time should be supported by the submission of stability data, if longer than 30 days. The cumulative holding times for all stages should not exceed 90 days; otherwise it should be supported by the submission of stability data. For an aseptically processed FPP, sterile filtration of the bulk and filling into final containers should be continuous.

Proposals for the reprocessing of materials should be scientifically justified. Any data to support this justification should be filed in this section (3.2.P.3.3).

The information above should be summarized in the QOS template and should reflect the production of the proposed commercial batches and not pilot-scale batches.

For the manufacture of sterile products, the class (e.g. A, B, C, etc.) of the areas should be stated for each activity (e.g. compounding, filling, sealing etc), as well as the sterilization parameters for equipment, container/closure, terminal sterilization etc.

Reference ICH Guideline: Q8, Q9, Q10

3.2.P.3.4 Controls of Critical Steps and Intermediates (name, dosage form)

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

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

Examples of applicable in-process controls include:

- granulations: moisture (limits expressed as a range), blend uniformity (e.g. low dose tablets), bulk and tapped densities, particle size distribution;
- solid oral products: average weight, weight variation, hardness, thickness, friability, and disintegration checked periodically throughout compression, weight gain during coating;
- semi-solids: viscosity, homogeneity, pH;
- transdermal dosage forms: assay of API-adhesive mixture, weight per area of coated patch without backing;
- metered dose inhalers: fill weight/volume, leak testing, valve delivery;
- dry powder inhalers: assay of API-excipient blend, moisture, weight variation of individually contained doses such as capsules or blisters;
- liquids: pH, specific gravity, clarity of solutions; and
- parenterals: appearance, clarity, fill volume/weight, pH, filter integrity tests, particulate matter, leak testing of ampoules, pre-filtration and/or pre-sterilization bioburden testing.

Reference ICH Guidelines: Q2, Q6A, Q8, Q9, Q10, WHO Technical Report Series, No. 929, Annex 5

3.2.P.3.5 Process Validation and/or Evaluation (name, dosage form)

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

For products that meet the criteria of an established generic product, a product quality review as outlined in Appendix 2 may be submitted in lieu of the information below.

The following information should be provided for all other products:

a) a copy of the process validation protocol, specific to this FPP.

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 after registration by the inspectors.

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

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

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

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

The process validation protocol should include inter alia the following:

- a reference to the current master production document;
- a discussion of the critical equipment;
- the process parameters that can affect the quality of the FPP (critical process parameters (CPPs)) including challenge experiments and failure mode operation;
- 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);
- the testing parameters/acceptance criteria including in-process and release specifications and including comparative dissolution profiles of validation batches against the batch(es) used in the bioavailability or biowaiver studies;
- the analytical procedures or a reference to appropriate section(s) of the dossier;
- the methods for recording/evaluating results; and
- the proposed time frame for completion of the protocol.

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

a) washing, treatment, sterilization and depyrogenation of containers, closures and equipment;

b) filtration of solutions;

c) lyophilization process;

d) leaker test of filled and sealed ampoules;

e) final inspection of the product; and

f) sterilization cycle.

The sterilization process used to destroy or remove microorganisms is probably the single most important process in the manufacture of parenteral FPPs. The process can make use of moist heat (e.g. steam), dry heat, filtration, gaseous sterilization (e.g. ethylene oxide), or radiation. It should be noted that terminal steam sterilization, when practical, is considered to be the method of choice to ensure sterility of the final FPP. Therefore, scientific justification for selecting any other method of sterilization 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 F_0 range, 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 processing of parenteral products that cannot be terminally sterilized, simulation process trials should be conducted. This involves filling containers with culture media under normal conditions, followed by incubation. Refer to current WHO guidelines for details.

Reference ICH Guideline: Q8, Q9, Q10, WHO Technical Report Series, No. 961, Annex 3

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

3.2.P.4.1 Specifications (name, dosage form)

The specifications for excipients should be provided.

The specifications from the applicant or 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 products submitted to Botswana, only excipients with an officially recognized pharmacopoeial monograph should be used. For innovator products the use of non-compendia excipients may be allowed if appropriately justified.

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

Skip testing is acceptable if justified (submission of acceptable results of five production batches).

For oils of plant origin (e.g. soy bean oil, peanut oil) 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).

The supplier with reference to the specific related product may submit information that is considered confidential directly to the MRA.

Other certifications of at-risk components may be required on a case-by-case basis.

If additional purification is undertaken on commercially available excipients details of the process of purification and modified specifications should be submitted.

Reference Guideline: Handbook of Pharmaceutical Excipients, Compendial monographs, and Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product.

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

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

Copies of analytical procedures from officially recognized compendial monographs do not need to be submitted.

Reference ICH Guidelines: Q2

3.2.P.4.3 Validation of Analytical Procedures (name, dosage form)

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

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

Reference ICH Guidelines: Q2

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

Justification for the proposed excipient specifications should be provided, where appropriate. A discussion of the tests that are supplementary to those appearing in the officially recognized compendial monograph should be provided.

3.2.P.4.5 Excipients of Human or Animal Origin (name, dosage form)

For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g., sources, specifications; description of the testing performed; viral safety data). (Details in 3.2.A.2).

The following excipients should be addressed in this section: lactose, 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.

Materials of animal origin should be avoided whenever possible.

When available, a CEP demonstrating TSE-compliance should be provided. A complete copy of the CEP (including any annexes) should be provided in Module 1.

Reference Guidelines: Handbook of Pharmaceutical Excipients, Compendial monographs, and Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product.

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

For excipients used for the first time in a drug product 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 drug substance format. (Details in 3.2.A.3).

Novel excipients are generally not accepted. For the purpose of this guideline, a novel excipient is one that has not been used (at a similar level and by the same route of administration) in a product approved by ICH or WHO.

Reference Guidelines: Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product.

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

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

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

As defined in ICH Q6A guideline, a specification is:
"a list of tests, references to analytical procedures and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which an API or FPP should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the API and / or FPP, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities."

A copy of the FPP specification(s) from the applicant (as well as the company responsible for the batch release of the FPP, if different from the applicant), dated and signed by authorized personnel (i.e. the person in charge of the quality control or quality assurance department) should be provided in the dossier. Two separate sets of specifications may be set out: after packaging of the FPP (release) and at the end of shelf life.

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):

- the standard declared by the applicant could be an officially recognized compendial standard (e.g. Ph.Int., BP, USP, JP) or a House (manufacturer's) standard or any other pharmacopoeia recognized by a specific MS

- the specification reference number and version (e.g. revision number and/or date) should be provided for version control purposes;

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

ICH's Q6A guideline outlines recommendations for a number of universal and specific tests and criteria for FPPs. Specifications should include, at minimum, tests for appearance, identification, assay, purity, performance tests (e.g. dissolution), physical tests (e.g. loss on drying, hardness, friability, particle size), uniformity of dosage units, and as applicable, identification and assay of antimicrobial or chemical preservatives (e.g. antioxidants) and microbial limit tests.

The following information provides guidance for specific tests that are not addressed by ICH's Q6A guideline:

- fixed-dose combination FPPs (FDC-FPPs):

    - analytical methods that can distinguish each API in the presence of the other API(s) should be developed and validated,

    - acceptance criteria for degradation products should be established with reference to the API they are derived from. If an impurity results from a chemical reaction between two or more APIs, its acceptance limits should in

general be calculated with reference to the worst case (the API with the smaller area under the curve). Alternatively the content of such impurities could be calculated in relation to their reference standards,

- a test and limit for content uniformity is required for each API present in the FPP at less than 5 mg or less than 5% of the weight of the dosage unit,

- for the API(s) present at equal or greater than 5 mg and equal or greater than 5% of the weight of the dosage unit, a test and limit for weight variation may be established in lieu of content uniformity testing;

- modified-release products: a meaningful API release method;
- inhalation and nasal products: consistency of delivered dose (throughout the use of the product), particle or droplet size distribution profiles (comparable to the product used in vivo studies, where applicable) and if applicable for the dosage form, moisture content, leak rate, microbial limits, preservative assay, sterility and weight loss;
- suppositories: uniformity of dosage units, melting point; and
- transdermal dosage forms: peal or shear force, mean weight per unit area, dissolution.

Unless there is appropriate justification, the acceptable limit for the API content of the FPP in the release specifications is ± 5% of the label claim (i.e. 95.0 – 105.0%)

For products such as tablets, capsules and suppositories where a test for uniformity of single dose preparations is required, a test and limit for content uniformity is required when the API is present in the FPP at less than 5 mg or less than 5% of the weight of the dosage unit. Otherwise, the test for mass uniformity may be applied.

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.

Any differences between release and shelf life tests and acceptance criteria should be clearly indicated and justified. Note that such differences for parameters such as dissolution are normally not accepted.

Reference ICH Guidelines: Q3B, Q3C,Q6A

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

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

Copies of the in-house analytical procedures used during pharmaceutical development (if used to generate testing results provided in the dossier) 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.

Tables for summarizing a number of the different analytical procedures and validation information (e.g. HPLC assay/impurity methods) can be found in the 2.3.R Regional information section of the QOS (i.e. 2.3.R.2). These tables should be used to summarize the analytical procedures used for determination of the assay, related substances and dissolution of the FPP.

Refer to section 3.2.S.4.2 of this guideline for additional guidance on analytical procedures.
Reference ICH Guidelines: Q2

3.2.P.5.3 Validation of Analytical Procedures (name, dosage form)

Analytical validation information, including experimental data, for the analytical procedures used for testing the drug product, 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 dossier) as well as those proposed for routine testing should be provided.

Tables for summarizing a number of the different analytical procedures and validation information (e.g. HPLC assay/impurity methods, GC methods) can be found in the 2.3.R Regional information section of the QOS (i.e. 2.3.R.2). These tables should be used to

summarize the validation information of the analytical procedures used for determination of the assay, related substances and dissolution of the FPP.

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. Performing duplicate analyses of one sample by both methods and providing the results from the study could accomplish this. For related compound methods, the sample analyzed should be the placebo spiked with related compounds at concentrations equivalent to their specification limits.

Reference ICH Guidelines: Q2.

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

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

Information should include strength and batch number, batch size, date and site of production and use (e.g. used in comparative bioavailability or biowaiver studies, preclinical and clinical studies (if relevant), stability, pilot, scale-up and, if available, production-scale batches) on

relevant FPP batches used to establish the specification(s) and evaluate consistency in manufacturing.

Analytical results tested by the company responsible for the batch release of the FPP (generally, the applicant or the FPP manufacturer, if different from the applicant) should be provided for not less than two batches of at least pilot scale, or in the case of an uncomplicated FPP (e.g. immediate-release solid FPPs (with noted exceptions), non-sterile solutions), not less than one batch of at least pilot scale and a second batch which may be smaller (e.g. for solid oral dosage forms, 25 000 or 50 000 tablets or capsules) of each proposed strength of the FPP. These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

The testing results should include the batch(es) used in the comparative bioavailability or biowaiver studies. Copies of the certificates of analysis for these batches should be provided in the dossier and the company responsible for generating the testing results should be identified.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as "all tests meet specifications". This should include ranges of analytical results, where relevant. For quantitative tests (e.g. individual and total impurity tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements such as "within limits" or "conforms" (e.g. "levels of degradation product A ranged from 0.2 to 0.4%"). Dissolution results should be expressed at minimum as both the average and range of individual results. Recommendations for conducting and assessing comparative dissolution profiles can be found in Appendix 1.

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

Reference ICH Guidelines: Q3B, Q3C, and Q6A.

3.2.P.5.5 Characterisation of Impurities (name, dosage form)

Information on the characterisation 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).

Reference ICH Guidelines: Q3B, Q5C, and Q6A.

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

Justification for the proposed drug product 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 dossier and does not need to be repeated here, although a cross-reference to their location should be provided.

ICH Q6A should be consulted for the development of specifications for FPPs.

Reference ICH Guidelines: Q3B, and Q6A.

3.2.P.6 Reference Standards or Materials (name, dosage form)

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

Reference ICH Guidelines: Q6A, WHO Technical Report Series, No. 943, Annex 3

3.2.P.7 Container Closure System (name, dosage form)

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

For non-functional secondary packaging components (e.g., those that neither provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

Suitability information should be located in 3.2.P.2.

The WHO Guidelines on packaging for pharmaceutical products (WHO Technical Report Series, No. 902, Annex 9, 2002) and the officially recognized pharmacopoeias should be consulted for recommendations on the packaging information for FPPs.

Descriptions, materials of construction and specifications (of the company responsible for packaging the FPP, generally the FPP manufacturer) should be provided for the packaging components that are:

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

Primary packaging components are those that are in direct contact with the API or FPP.

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.

Information to establish the suitability (e.g. qualification) of the container closure system should be discussed in Section 3.2.P.2. Comparative studies may be warranted for certain changes in packaging components (e.g. comparative delivery study (droplet size) for a change in manufacturer of dropper tips).

3.2.P.8 Stability (name, dosage form)

3.2.P.8.1 Stability Summary and Conclusion (name, dosage form)

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

The Botswana stability guideline Stability testing of active pharmaceutical ingredients and finished pharmaceutical products should be consulted for recommendations on the core stability data package required for the prequalification of APIs and FPPs.

As outlined in the Botswana stability guideline, 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.

Stress testing

As outlined in the Botswana stability guideline, photostability testing should be conducted on at least one primary batch of the FPP if appropriate. If "protect from light" is stated in one of the officially recognized pharmacopoeia for the API or FPP, 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. Additional stress testing of specific types of dosage forms may be appropriate (e.g. cyclic studies for semi-solid products, freeze-thaw studies for liquid products).

Accelerated, intermediate (if necessary) and long-term testing

Stability data must demonstrate stability of the medicinal product throughout its intended shelf-life under the climatic zone III and IVa as prevalent in Botswana. Merely applying the same requirements applicable to other markets could potentially lead to substandard products, e.g. stability studies conducted for countries in Climatic Zone I/II when the products are supplied in Botswana. Studies done at any other stability conditions will need to be justified and should be supported with appropriate evidence.

Other storage conditions are outlined in ICH guidelines for FPPs packaged in impermeable and semi-permeable containers and those intended for storage in a refrigerator and in a freezer.

Unless otherwise justified, the minimum data required at the time of submitting the dossier (in the general case):

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

Applicants should consult BoMRA on acceptability of six month long term stability data at the time of submission. In any case, minimum of 12 month long term stability data should be available at the time of registration.

Drug products packaged in semi-permeable containers.

Storage temperature (°C)	Relative humidity (%)	Minimum time period (months)
Accelerated 40 ± 2	25	6
Long term 30 ± 2	35 ± 5	12

To establish the shelf life, data should be provided on three production batches for the full-proposed shelf life. If not available, submit not less than two batches of at least pilot scale, or in the case of an uncomplicated FPP (e.g. immediate-release solid FPPs (with noted exceptions), non-sterile solutions), not less than one batch of at least pilot scale and a second batch which may be smaller (e.g. for solid oral dosage forms, 25 000 or 50 000 tablets or capsules) of each proposed strength of the FPP with the commitment to provide for production batches. The pilot batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

The stability-testing programme should be summarized and the results of stability testing should be reported in the dossier and summarized in the tables in the QOS. Bracketing and matrixing of proportional strengths can be applied, if scientifically justified.

For sterile products sterility should be reported at the beginning and end of shelf life. For parenteral products, subvisible particulate matter should be reported frequently, but not necessarily at every test interval. Bacterial endotoxins need only be reported at the initial test interval. Weight loss from plastic containers should be reported over the shelf life.

Any in-use period and associated storage conditions should be justified with experimental data, for example after opening, reconstitution and/or dilution of any sterile and/or multidose products or after first opening of FPPs packed in bulk multidose containers (e.g. bottles of 1000ʺs). If applicable, the in-use period and storage conditions should be stated in the product information.

The information on the stability studies should include details such as

- storage conditions;
- strength;
- batch number, including the API batch number(s) and manufacturer(s);
- batch size;
- container closure system including orientation (e.g. erect, inverted, on-side) where applicable; and
- completed (and proposed) test intervals.

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 and any trends that were observed. For quantitative tests (e.g. individual and total degradation product tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements such as "within limits" or "conforms". Dissolution results should be expressed at minimum as both the average and range of individual results.
Applicants should consult ICH's Q1E guideline for details on the evaluation and extrapolation of results from stability data (e.g. if significant change was not observed within 6 months at accelerated condition and the data show little or no variability, the proposed shelf-life could

be up to two times the period covered by the long-term data, but should not exceed the long-term data by 12 months).

Proposed storage statement and shelf life

The proposed storage statement and shelf-life (and in-use storage conditions and in-use period, if applicable) for the FPP should be provided.

The recommended labelling statements for use, based on the stability studies, are provided in the Botswana stability guideline.

Reference ICH Guidelines: Q1A, Q1B, Q1C, Q1D, Q3B and Q6A

3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment (name, dosage form)

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

Primary stability study commitment

When available long-term stability data on primary batches do not cover the proposed shelf-life granted at the time of assessment of the dossier, a commitment should be made to continue the stability studies in order to firmly establish the shelf-life. A written commitment (signed and dated) to continue long-term testing over the shelf-life period should be included in the dossier.

Commitment stability studies

The long-term stability studies for the Commitment batches should be conducted through the proposed shelf life on at least three production batches of each strength in each container closure system. Where stability data was not provided for three production batches of each strength, a written commitment (signed and dated) should be included in the dossier.

Ongoing stability studies

An ongoing stability programme is established to monitor the product over its shelf life and to determine that the product remains and can be expected to remain within specifications

under the storage conditions on the label. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every container closure system, if relevant, should be included in the stability programme (unless none is produced during that year). Bracketing and matrixing may be applicable. A written commitment (signed and dated) to this effect should be included in the dossier.
Any differences in the stability protocols used for the primary batches and those proposed for the commitment batches or ongoing batches should be scientifically justified.

Reference ICH Guidelines: Q1A

3.2.P.8.3 Stability Data (name, dosage form)

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

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

The actual stability results/reports used to support the proposed shelf life should be provided in the dossier. For quantitative tests (e.g. individual and total degradation product tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements such as "within limits" or "conforms". Dissolution results should be expressed at minimum as both the average and range of individual results.

Reference ICH Guidelines: Q1A, Q1B, Q1C, Q1D, Q1E, and Q2

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment (name, manufacturer)

Not applicable (i.e. not a biotech product).

3.2.A.2 Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)

3.2.A.3 Novel Excipients

3.2.R REGIONAL INFORMATION

3.2.R.1 Production documentation

Copy of the batch manufacturing record including the ingredient analytical reports, in process control tests reports, intermediate product test reports, reconciliation records and a certificate of analysis for the batch must be presented.

3.2.R.1.1 Executed production documents

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

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

Copies of executed manufacturing records provided should be in English or translated into English.

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 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, 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, LOD, weight variation, hardness, disintegration time, weight gain during coating, leaker test, minimum fill, clarity, filter integrity checks) and specifications;

g) sampling plan with regard to the:

   i. steps where sampling should be done (e.g. drying, lubrication, 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, maximum holding times);

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

j) theoretical and actual yield;

k) compliance with the GMP requirements.

Reference documents: WHO Technical Report Series, No. 961

3.2.R.2 Analytical procedures and validation information

Where validation is still to be completed, a summary of the studies intended to be conducted should be provided.

The tables presented in section 2.3.R.2 in the QOS 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.

3.2.R.3 Bioequivalence trial information form (BTIF)

3.2.R.3.1 A completed BTIF should be submitted both in hard copy and electronic (word format)

3.2.R.3.2 Biowaiver requests in relation to conducting comparative bioavailability study

A completed Biowaiver Application Form should be submitted (word format)

Requirements for biopharmaceutic studies are described in the following:

- EMA Guideline on Investigation of Bioequivalence (also covers additional strength, BCS based biowaivers), EMA Guideline on Bioanalytical Method Validation (Bioanalytical method validation, presentation of biopharmaceutical and bioanalytical data, and pharmacokinetic and clinical evaluation of modified release dosage forms). https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-efficacy-safety-clinical-pharmacology-pharmacokinetics

- ICH M9 on biopharmaceutics classification system based biowaivers https://www.ema.europa.eu/en/ich-m9-biopharmaceutics-classification-system-based-biowaivers

- WHO guidances for organizations performing in vivo bioequivalence studies https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/regulatory-standards/trs966-annex9-invivo-bioequivalence-studies.pdf?sfvrsn=510cfeec_2

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.

APPENDIX I - RECOMMENDATIONS FOR CONDUCTING AND ASSESSING COMPARATIVE DISSOLUTION PROFILES

The dissolution measurements of the two FPPs (e.g. test and reference (comparator), or two different strengths) should be made under the same test conditions. A minimum of three time points (zero excluded) should be included, the time points for both reference (comparator) and test product being the same. The sampling intervals should be short for a scientifically sound comparison of the profiles (e.g. 5, 10, 15, 20, 30, 45 (60, 90, 120) minutes). Inclusion of the 15 minute time point in the schedule is of strategic importance for profile similarity determinations (very rapidly dissolving scenario). For extended-release FPPs, the time points should be set to cover the entire time period of expected release, e.g. 1, 2, 3, 5 and 8 hours for a 12-hour release and additional test intervals for longer duration of release.

Studies should be performed in at least three (3) media covering the physiological range, including pH 1.2 hydrochloric acid, pH 4.5 buffer and pH 6.8 buffer. Compendia buffers are recommended. The Authority recognises the International Pharmacopeia, British Pharmacopeia, United Stated Pharmacopeia, and the European Pharmacopeia. Water may be considered as an additional medium, especially when the API is unstable in the buffered media to the extent that the data is unusable.

If both the test and reference (comparator) products show more than 85% dissolution in 15 minutes, the profiles are considered similar (no calculations required). Otherwise:

Similarity of the resulting comparative dissolution profiles should be calculated using the following equation that defines a similarity factor (f2):

$$f2 = 50LOG\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(Rt - Tt)^2\right]^{-0.5} x100\}$$

- where Rt and Tt are the mean percent API dissolved in reference (comparator) and test product, respectively, at each time point. An f2 value between 50 and 100 suggests the two dissolution profiles are similar;

- a maximum of one time-point should be considered after 85% dissolution of the reference (comparator) product has been reached. In the case where 85% dissolution cannot be reached due to poor solubility of the API, the dissolution should be conducted until an asymptote (plateau) has been reached;

- at least 12 units should be used for each profile determination. Mean dissolution values can be used to estimate the similarity factor, f2. To use mean data, the % coefficient of variation at the first time point should be not more than 20% and at other time points should not be more than 10%;

- when delayed-release products (e.g. enteric coated) are being compared, the recommended conditions are acid medium (pH 1.2) for 2 hours and buffer pH 6.8 medium;

- when comparing extended-release beaded capsules, where different strengths have been achieved solely by means of adjusting the number of beads containing the API, one condition (normally the release condition) will suffice; and

- surfactants should be avoided in comparative dissolution testing. A statement that the API is not soluble in any of the media is not sufficient and profiles in absence of surfactants should be provided. The rationale for the choice and concentration of surfactant should be provided. The concentration of the surfactant should be such that the discriminatory power of the test will not be compromised.

APPENDIX 2 – PRODUCT QUALITY REVIEW REQUIREMENTS FOR *ESTABLISHED GENERIC PRODUCTS*

For an established multisource 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.

A product quality review should be submitted with the objective of verifying the consistency of the quality of the FPP and its manufacturing process.

Rejected batches should not be included in the analysis but must be reported separately together with the reports of failure investigations, as indicated below.

Reviews should be conducted with not less than 10 consecutive batches manufactured over the period of the last 12 months, or, where 10 batches were not manufactured in the last 12 months, not less than 25 consecutive batches manufactured over the period of the last 36 months and should include at least:

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

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

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

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

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

6. A review of the results of the stability-monitoring programme.

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

8. A review of the adequacy of previous corrective actions.

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

Notes

Reviews must include data from all batches manufactured during the review period.

Data should be presented in tabular or graphical form (i.e. charts or graphs), when applicable.

The above is specific to the dossier assessment process requirements and does not relieve the applicant of related GMP requirements.