PHARMACY AND MEDICINES REGULATORY AUTHORITY

Quality Medicines for Malawi

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GUIDANCE ON SUBMISSION OF DOCUMENTATION FOR REGISTRATION OF A MULTISOURCE (GENERIC) FINISHED PHARMACEUTICAL PRODUCT (FPP): QUALITY PART IN THE COMMON TECHNICAL DOCUMENT (CTD) FORMAT

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ABBREVIATIONS

API	Active Pharmaceutical Ingredient
ARV	Antiretroviral
APIMF	Active Pharmaceutical Ingredient Master File
BAN	British Approved Name
BCS	Biopharmaceutical Classification System
BE	Bioequivalence
BP	British Pharmacopoeia
BTIF	Bioequivalence Trial Information Form
CAS	Chemical Abstracts Service Registry Number
CD	Controlled Drug
CPP	Certificate of Pharmaceutical Product
CEP	European Certificate of Suitability
CoA	Certificate of Analysis
CTD	Common Technical Document
DSC	Differential Scanning Calorimetry
DRA	Drug Regulatory Authority
EOI	Expression of Interest
EU	European Union
FDA	United States Food and Drug Administration
FDC	Fixed Dose Combination
FPP	Finished Pharmaceutical Product
GC	Gas Chromatography
GSL	General Sales List
HPLC	High Pressure Liquid Chromatography
ICH	International Conference on Harmonisation
INN	International Non-proprietary Name
IR	Infrared Spectroscopy
GMP	Good Manufacturing Practice
Int.Ph.	International Pharmacopoeia
JP	Japanese Pharmacopoeia
LOD	Loss on drying
NF	National Formulary

NLT	Not Less Than
NMT	Not More Than
SADC	Southern African Development Community
SI 150	Statutory Instruments 150 of 1991
SmPC	Summary of Product Characteristics
SMACS	WHO pharmaceutical starting materials certification scheme
SRA	Stringent Regulatory Authority
SST	System Suitability Test
RSD	Relative Standard Deviation
TCL	Thin Layer Chromatography
TSE	Transmissible Spongiform Encephalopathy
P	Pharmacy Only Medicines
PDs	Product Dossiers
PDE	Permissible Daily Exposure
Ph. Eur	European Pharmacopoeia
Ph Int.	International Pharmacopoeia
PIL	Patient Information Leaflet
PIM	Pharmacist Initiated Medicines
POM	Prescription Only Medicines
PQIT	Product Quality Information Template
QA	Quality Assurance
QIS	Quality Information Summary
QOS	Quality Overall Summary
PMRA	Pharmacy and Medicines Regulatory Authority
PMRA-QOS	PMRA Quality Overall Summary
QTPP	Quality Target Product Profile
RH	Relative Humidity
USAN	United States Adopted Name
USP	United States Pharmacopoeia
USD	United States Dollars
USFDA	United States Food and Drug Administration
WHO	World Health Organisation
WHO TRS	WHO Technical Report Series
XRPD	X-Ray Powder Diffraction

GLOSSARY

The definitions provided below apply to the words and phrases used in these guidelines. Although an effort has been made to use standard definitions as far as possible, they may have different meanings in other contexts and documents. The following definitions are provided to facilitate interpretation of the guidelines.

Active pharmaceutical ingredient (API)
Any substance or combination of substances used in a finished pharmaceutical product (FPP), intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have a direct effect in restoring, correcting or modifying physiological functions in human beings.

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 (ref. ICH Q7). See also *starting materials for synthesis*.

Applicant
Means the person or entity by, or on whose behalf, an application for registration is made.

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 37ºC (ref. WHO Technical Report Series, No. 937, Annex 7, 2006).

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 (ref. WHO Technical Report Series, No. 953, Annex 2, 2009).

Comparator product
A pharmaceutical product with which the generic product is intended to be interchangeable in clinical practice. The comparator product will normally be the innovator product for which efficacy, safety and quality have been established (ref. WHO BE Guidelines). The selection of the comparator product is based on the information presented under Guidance on Bioequivalence Studies available on the Prequalification website or as provided in the USFDA Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Established multisource (generic) 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.

Existing API
An API that is not considered a new active substance that has been previously approved through a finished product by a stringent regulatory authority, PMRA or WHO, but requires the filing of a dossier. This would include, for example, new PDs and variations to multisource products.

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

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

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

Multisource (generic) pharmaceutical products
Pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable (WHO Technical Report Series, No. 937, Annex 7, 2006).

Officially recognized pharmacopoeia (or compendium)
Those pharmacopoeias recognized by the PMRA (i.e. The International Pharmacopoeia (Ph.Int.), the European Pharmacopoeia (Ph.Eur.), the British Pharmacopoeia (BP) and the United States Pharmacopeia (USP)).

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.

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

Primary batch
A batch of an API or FPP used in a stability study, from which stability data are submitted in a registration application for the purpose of establishing a retest period or shelf-life. Primary batch requirements are outlined in 3.2.S.7.1 and 3.2.P.8.1 for the API and FPP, respectively.

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,

Starting materials for synthesis
Materials that mark the beginning of the manufacturing process as described in an application or in an 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*

INTRODUCTION

Background

These guidelines are an update to the PMRA Registration Guidelines published in 2002. Changes in regulatory practice and policy have been made since 2002 which warrants change in regulations. The improvements are based on the *World Health Organisation (WHO) Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): quality part* and on the International Conference on Harmonisation guidelines.

Through the International Conference on Harmonisation (ICH) process, considerable harmonisation has been achieved on the organisation of the registration documents with the issuance of the common technical document (CTD) guideline. This recommended CTD format for submitting registration applications has become widely accepted by regulatory authorities the world over. This document provides recommendations on the format and presentation for these types of product dossiers.

This document, *Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): quality part,* provides recommendations on the quality information for active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs) that should be submitted to PMRA 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. It is also important to note that PMRA may request information or material, or define conditions not specifically described in this guidance, in order to adequately assess the quality of a pharmaceutical product.

The content of this guideline should be read in conjunction with relevant information described in other existing PMRA, WHO or ICH reference documents and guidelines. Scientific literature may be appropriate to fulfill the requirements for some of the information or parameters outlined in this guideline (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.

Applicants interested in having their FPPs evaluated for registration in Malawi should submit a product dossier reflecting the data and information requested below. The current version of any guideline or pharmacopoeia referred to in this guideline shall be applicable in all instances. Any deviations must be highlighted, justified and require approval by the PMRA.

When applicants are applying for registration of fixed dose combination (FDC) products they should address all the requirements of the *WHO TRS 929 Guideline for Registration of Fixed Dose Combination Medicinal Products* in addition to the guidelines below.

An application for registration of a medicine may be made by:

- The prospective holder of the marketing authorisation/registration, hereinafter referred to as the applicant
- A nominee of the applicant who must submit evidence of power of attorney

Objectives

This guideline is intended to:

a) assist applicants on the preparation of applications for registration (product dossiers) for multisource (generic) products by providing clear general guidance on the format of these dossiers;

b) fully adopt the modular format of the *Common Technical Document - Quality (M4Q)* as developed by ICH; and

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 by applicants and the subsequent assessment procedures by PMRA.

Scope

This guideline applies to applications for registration for multisource (generic) pharmaceutical products containing APIs of synthetic or semi-synthetic origin. Fermentation, biological, biotechnological and herbal APIs are covered by other guidelines.

General Principles

To facilitate the preparation of the application for registration (product dossier), this guideline is organised in accordance with the structure of the *Common Technical Document – Quality (M4Q)* guideline, as developed by ICH.
The text of the M4Q (CTD-Q) guideline has been re-stated in this guideline, with minor modifications to accommodate PMRA terminology and include certain text that would be appropriate for multisource pharmaceutical products, notably:

- "Drug substance" is replaced with "active pharmaceutical ingredient" or "API";
- "Drug product" is replaced with "finished pharmaceutical product" or "FPP";
- "Combination product" is replaced with "fixed-dose combination" or "FDC";
- "clinical batches" is replaced with "comparative bioavailability or biowaiver batches".

GUIDANCE ON THE FORMAT AND PRESENTATION

Guidance on format

The CTD is organised into five modules. Module 1 is region/country-specific. Modules 2, 3, 4 and 5 are intended to be common for all regions. This section provides an overview of module contents for a multisource (generic) finished pharmaceutical product in greater detail.

a) Module 1- Administrative information and prescribing information:

- This module should contain documents specific to Malawi; for example, application forms, fees, package inserts and the proposed label for use in Malawi.
- A summary of the bioequivalence/bioavailability information should be provided according to PMRA Guidelines for the submission of documentation for the demonstration of interchangeability between generic products (Bioequivalence).

b) Module 2 - CTD summaries:

- This module should begin with a general introduction to the pharmaceutical product, including its pharmacological class, mode of action and proposed clinical use. In general, the Introduction should not exceed one page.
- A summary of the quality information should be provided according to the PMRA Quality overall summary (PMRA QOS) template.
- The organization of these summaries is described in Guidelines for ICH M4Q, M4S and M4E.

c) Module 3 - Quality:

- Information on quality should be presented in the structured format described in Guidelines ICH M4Q and in this guidance

d) Module 4 - Non-clinical study reports:

- Generally not applicable for multisource products (some exceptions may apply).

e) Module 5 - Clinical study reports:

- The human study reports and related information should be presented in the order described in Guidelines ICH M4E and the PMRA guidelines on bioequivalence.

Table 1: Modular format of application for registration of multisource products in CTD format

Module 1 – Administrative information and prescribing information
1.0 Cover letter
1.1 Table of contents of the application including Module 1 (Modules 1-5
1.2 Application information:
1.2.1 Completed, signed and dated FORM 8A application form in triplicate (see Annex I)
1.2.2 Declaration by the applicant
1.2.3 Proof of Payment of the appropriate fees
1.2.4 Manufacturing and marketing authorisation(s)/international registration status and/or the WHO certificate of pharmaceutical product (CPP)
1.2.5 Copy of certificate(s) of suitability of the European Pharmacopoeia (CEP) (including any annexes)
1.2.6 Proof of compliance with current Good Manufacturing Practices (cGMP)
1.2.7 Declaration letter stating that any subsequent inspection did not reveal non-conformance to GMP requirements.
1.2.8 Biowaiver requests in relation to conducting a comparative bioavailability study

1.3 Product information:
1.3.1 Summary of product characteristics (SmPC)
1.3.2 Labelling (primary and secondary packaging)
1.3.3 Package insert and patient information leaflet
1.4 Regional summaries:
1.4.1 Bioequivalence Trial Information form (BTIF)
1.4.2 Quality information summary (QIS)
1.5 Electronic review documents (e.g. product information, BTIF, QIS, PMRA-QOS)
1.6 Samples (e.g. FPP, device(s), certificates of analysis)
1.8 Checklist
1.9 Letter of authorization from the applicant appointing individual responsible from communication with PMRA
1.10 Declaration copy that the information provided is true.
Module 2 – Common technical document (CTD) summaries
2.1 CTD Table of contents (Modules 2-5)
2.2 CTD Introduction
2.3 Quality overall summary – product dossier (QOS-PD)
2.4 Non-clinical overview – generally not applicable for multisource products (some exceptions may apply)
2.5 Clinical overview
2.6 Non-clinical written and tabulated summaries – generally not applicable for multisource products (some exceptions may apply)
2.7 Clinical summary – generally not applicable for multisource products
Module 3 – Quality
3.1 Table of contents of Module 3
3.2 Body of data
3.3 Literature references
Module 4 – Non-clinical study reports – generally not applicable for multisource products (some exceptions may apply)
4.1 Table of contents of Module 4
4.2 Study reports
4.3 Literature references

Module 5 – Clinical study reports
5.1 Table of contents of Module 5
5.2 Tabular listing of all clinical studies
5.3 Clinical study reports
5.3.1 Reports of biopharmaceutical studies
5.3.7 Case report forms and individual patient listings
5.4 Literature references

Text and tables should be prepared using margins that allow the document to be printed on A4 paper. The left-hand margin should be sufficiently large that information is not obscured by the method of binding. Font sizes for text and tables should be of a style and size that are large enough to be easily legible, even after photocopying. Times New Roman, 12-point font is recommended for narrative text. Line spacing should be 1.0.

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

All application forms must be completed in English.

Guidance on presentation

Applicants are required to submit one hard copy of module one and two electronic copies of the whole application.

With regards to electronic copy, each section of the dossier should be in its folder with subsection being submitted as a separate document or one document with table of contents having hyperlink.

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

There may be a number of instances where repeated sections can be considered appropriate. Whenever a section is repeated, it should be made clear what the section refers to by creating a distinguishing title in parentheses following the M4Q (CTD-Q) guideline heading, e.g. 3.2.S Drug substance (or API) (name, Manufacturer A).

The 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 for registration, 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. One complete copy of the application form, 8A, for registration 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.

Additional guidance on sections to be included in Module 1

Cover letter

The cover letter submitted with the application for registration should include a clear statement from the responsible person submitting the dossier, indicating the contact details (telephone number, e-mail, and fax) of the person to whom all correspondence should be addressed.

A completed and signed FORM 8A Form (see Annex 1)

A completed, signed and dated FORM 8A form should be submitted for each FPP. A copy of the form can be obtained from the PMRA website: www.pmra.mw. For clarity, the following considerations apply in determining whether the FPP requires one or separate applications

a) Tablets/Capsules/Suppositories/Lozenges:
    i) Different pack-sizes of the same strength and formulation will require one application
    ii) ii) Different strengths and/or formulations will require separate applications.

b) Syrups/Elixirs/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.

c) 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) Dry powders or crystals etc. of the same respective mass, packaged in ampoules and single dose vials 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 one application;
   vi) Dental cartridges containing fluids of different volumes will require one application;
   vii) Ampoules containing "water for injection", but of different volumes 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 masses 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 one application;
   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 one application provided the following data are submitted: -

- Characteristics of the rubber stopper;
- Specifications for the glass;
- A comprehensive manufacturing process with particular reference to the washing and sterilization cycles and apparatus used; - Data on particulate matter (contamination);
- Stability data with reference to the effect of the pH of the solution in their respective containers.

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 category of distribution (scheduling status), or different pharmacological classification or have any other restrictions imposed other than the original application, will require separate registration.

d) Different applicants/proprietary names for the same formula;
   i) Same formula applied under different proprietary names will require separate applications.
   ii) Same formula from different applicants will require separate applications.

Declaration by the applicant

A declaration should be made by the applicant or a responsible person nominated by the applicant and who has the requisite skills and necessary qualifications. It is stressed that only a person who can attest to the accuracy of the contents in the application should sign on behalf of the applicant. False / misleading declarations will among others lead to rejection of the product, deregistration of the product if registered or prosecution.

Failure to make the declaration will lead to rejection of the application.

Declaration form from authorized person

Screening Checklist

A screening checklist in Annex 2 should be completed by the applicant. The Authority will assess the application for completeness upon submission before it is accepted for evaluation by PMRA. Incomplete applications will be rejected and the applicant requested to submit a complete application. The Authority may charge a re-submission fee for products that fail screening.

Proof of payment of appropriate fees

A copy of the invoice or proof of payment of registration fees should be attached to the application for registration.

Applicants should consult the current fee schedule for the correct and appropriate fee.

Unless the full application fee is received, the application will not be accepted. Applicants can remit payment of fees in telegraphic transfers and direct deposit into the Authority account. Applicants are further advised to specify very clearly in their instructions to the bank that such direct deposits are for application for registration of a medicine to avoid unnecessary delays.

Note that the application fee covers the cost of evaluating the initial submission and a single laboratory analysis of the product sample. Samples that require repeat analysis after failure of the first analysis, or as a result of modification or revalidation of the analytical method, attract an additional re-analysis fee. Any amendments to the original submission will attract amendment fees according to the gazetted fee schedule. The application fee excludes the GMP inspection fees, for which a separate charge is applicable.
Fees once received are not refundable, including those for rejected applications or voluntary withdrawals by the applicant.

Manufacturing and marketing authorisation(s)/international registration status

List the countries in which:

- the FPP (or set of FPPs) has been granted a marketing authorisation;
- the FPP (or one or more of the set of FPPs) has been withdrawn from the market; and • an application for the marketing of the FPP (or one or more of the set of FPPs) has been rejected, deferred or withdrawn

The details of registration in the country of origin are required. Reasons for non-registration should be stated if the medicine is not registered in the country of origin.
Registration status in the country of manufacture should be indicated including any withdrawal, cancellations, suspension / revocations. The reasons for these should also be indicated.

For further guidance see Section 3.2.P.3.1.

Summary of Product Characteristics (SmPC)

The Summary of Product Characteristics format in Annex III should be used.

Copies of all package inserts and any information intended for distribution with the product to the patient should be submitted. These should be written in English, be legible and comprehensible.

The presence of alcohol in the product must be declared, and the concentration stated on the label, the package insert and in the patient information leaflet.

The Authority will determine the appropriate category for distribution of a medicine as set out in regulations of medicines

The categories are:

a) Controlled Drugs (abbreviated as CD) - products containing ingredients stated as such in the legislation and which may be subject to control by the International Narcotics Board.
b) Prescription Only Medicines (POM) – medicines belonging to this category are available on prescription only
c) Pharmacist Initiated Medicines (P.I.M) – medicines that may be initiated and dispensed by a pharmacist without a prescription
d) Pharmacy Drugs (P) - these products are available from licensed medicine stores and pharmacies only
e) General Sales List (GSL) - Medicines in this category are available in pharmacies, dispensaries and all trade supermarkets.

Labelling (Primary and secondary packaging)

The Primary Packaging Label should comply with the Pharmacy and Medicines Regulatory Authority (Medicines Registration) Regulations with at least the following:

a) The name of the FPP
b) Route of administration

c) A list of API(s) (using INNs if applicable) with the amount of each present in a dosage unit, and a statement of the net contents of the container, e.g. number of dosage units, weight or volume
d) List of excipients known to be of safety concern for some patients, e.g. lactose, gluten, metabisulfites, parabens, ethanol
e) Instruction on use
f) The batch number assigned by the manufacturer
g) The manufacturing AND expiry date in an un-coded form
h) Storage conditions or handling precautions that may be necessary. The labelled storage conditions should be achievable in practice in the distribution network
i) Directions for use, and any warnings or precautions that may be necessary
j) The name and physical address of the manufacturing site(s)
k) For containers of capacity less than or equal to 10 ml that are marketed in an outer pack such as a carton, and the outer pack bears all the required information, the immediate container need only contain items (a), (b), (c), (f) and (g) —or a logo that unambiguously identifies the company— and the name of the dosage form or the route of administration

For Blisters and strips, as a minimum, the following information should be stated:

a) Name, strength and pharmaceutical form of the FPP
b) Name of the manufacturer, company or person responsible for placing the product on the market
c) The batch number assigned by the manufacturer
d) The expiry date in an un-coded form

The Secondary/Outer Packaging Label should also contain all the information in section 1.3.2.

Note: For all labelling, the generic name should be more prominent than the trade name. Provision for Malawian registration details i.e. category for distribution and registration number, should be made on the label.

Package insert

The package insert should comply with the Pharmacy and Medicines Regulatory Authority's product information guidelines with at least the following:

a) the name and address of the applicant;
b) the name and address of the manufacturer;
c) the approved name of the active ingredient of the medicine which shall be of greater size and prominence than the proprietary name (trade mark), if any, of the medicine;
d) the house-mark, if any, of the principal or manufacturer of the medicine;

e) the quantity and strength of the active ingredient of the medicine;
f) the name and percentage of any bacteriostatic or bactericidal agent which is added to the medicine as a preservative;
g) the strength of the medicine where applicable;
h) the requirements for the method of storage or other necessary precautions for the preservation of the medicine;
i) the category of distribution of the medicine which may be represented by words or symbols as set out in the Sixth Schedule;
j) the pharmacological classification of the medicine;
k) the dosage of the medicine and the directions for use;
l) the description of the pharmacological action of the medicine;
m) indications of the medicine;
n) contra – indications of the medicine;
o) warnings relating to the use of the medicine and such warning shall be printed in a colour as approved by the Authority;
p) the side-effects and special precautions of the medicine;
q) known symptoms of over dosage and particulars of its treatment;
r) the identification of the medicine;
s) the form in which the medicine is presented, whether tablet, capsule, liquid, etc., and the colour thereof;
t) the date of publication of the package insert;
u) any necessary warning concerning the administration or use of the medicine by children, old people, pregnant women or patients suffering from certain diseases, or the use of the medicine in conjunction with the consumption of alcohol or any particular food or any other medicine;
v) a summary of relevant information concerning the purpose and the beneficial, detrimental, injurious or other effects of the medicine, and the possible dangers that may arise from the prolonged use of the medicine;
w) relevant information, including particulars in regard to a specific medicine as an antidote (if known), concerning the treatment of a patient in cases where an overdose of the medicine has been administered or where a patient reacts adversely to the medicine;
x) any other particulars or warning notices as may be directed by the Authority.

For multisource (generic) products, the applicant shall not include the proprietary name in the body of text of the package insert unless clinical studies were conducted. Only the nonproprietary name should be used. Provision for Malawian registration details should be made on the package insert.

Applicant is required to submit the actual package insert and A4 size copies in English.

Electronic Review Documents

Electronic submission of documentation on electronic storage media e.g. CD or DVD should be submitted in Microsoft Word (required for templates/summaries, e.g. QOS–PD, QIS, BTIF) or text-selectable PDF format (other documentation).

Product Samples (e.g. FPP, device[s])

Samples and certificates of analysis of the FPP(s) and devices(s) should be provided to enable visual inspection of the pharmaceutical product, the packaging materials and the label as well as comparison of the data with that in the SmPC, labelling and the package insert.

Draft labelling may be submitted at the time of dossier submission when labelling for marketing has not been finalised. Applicants should provide samples of the FPP in its final container and labelling as intended for presentation to the Malawian market or closest reference packs when the labelling for marketing has not been finalised. Samples of the FPP in the market container should be provided to allow examination by the evaluators (assessors). In addition to the above, additional samples should be submitted for laboratory analysis by the National Quality Control Laboratory. The quantities of samples that should be submitted to the Authority for laboratory analysis should, in general, be twice the amount that is normally required for carrying out the full finished product analytical tests by the applicant's own quality control laboratory. This amount will enable repeat testing, if necessary. The precise quantities of samples required are indicated in *Annexure IV*. The applicants should always submit reference analytical standards and their certificates of analysis to allow the PMRA laboratory to expedite the analysis.

QUALITY SUMMARIES

3.1 Module 2.3: Quality Overall Summary – Product Dossiers (QOS-PD)

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

The QOS should include sufficient information from each section to provide the Quality assessor with an overview of Module 3. The QOS should also emphasise critical key parameters of the product and provide, for instance, justification in cases where guidelines were not followed. The QOS should include a discussion of key issues that integrates information from sections in the Quality Module and supporting information from other Modules (e.g., qualification of impurities

via toxicological studies), including cross-referencing to volume and page numbers in other Modules.

The PMRA *Quality Overall Summary – Product Dossiers (QOS-PD)* template should be completed for multisource pharmaceutical products containing APIs of synthetic or semisynthetic origin and their corresponding FPPs.

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

The use of tables to summarise 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 summarise information. Other approaches to summarise the information can be used if they fulfil the same purpose.

3.2 Module 1.4.2: Quality Information Summary (QIS)

The QIS template should be completed to provide a *condensed summary* of the *key quality information* for the PD and constitutes part of the submission package. The QIS provides an accurate record of technical data in the PD. The QIS is a condensed version of the QOS-PD and represents the final agreed upon *key API and FPP information* from the PD assessment (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-PD filed with the PD. 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 PD.

The QIS will serve as an official reference document in the course of GMP inspections, variation assessments and re-registration assessments as performed by PMRA.

MODULE 3: QUALITY

4.1 Table of contents of Module 3

A Table of Contents for the filed product dossier should be provided.

4.2 Body of data

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

The API information can be submitted to PMRA in one of the following two options:
Option 1: Certificate of Suitability of the European Pharmacopoeia (CEP), including all its annexes;
Option2: Full details in the PD.

The applicant should clearly indicate at the beginning of the API section (in the PD and in the PMRA 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: Certificates of Suitability of the European Pharmacopoeia (CEP)***

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

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

Along with the CEP, the applicant should supply the following information in the dossier, with data summarised in the PMRA 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. solubility 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 tests in addition to those in the CEP and Ph.Eur. monograph.
- *3.2. S.4.4 Batch analysis* - results from three batches of at least pilot scale, demonstrating compliance with the FPP manufacturer's API specifications.
- *3.2. S.6 Container closure system* - specifications including descriptions and identification of primary packaging components. Exception: where the CEP specifies a retest period.
- *3.2. S.7 Stability* - exception: where the CEP specifies a retest period that is the same as or of longer duration than the retest period proposed by the applicant.

In the case of sterile APIs, it should be noted that sterilization of the API is generally regarded by the PMRA as part of finished product manufacture. Therefore data on the sterilization process of the API, including validation data, should be included in the application for registration.

• ***Option 2: Full details in the PD***

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

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

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

Where an API is formed in situ during FPP manufacture (e.g. by chemical reaction), both the starting material(s) and the in situ formed API should be described (say for instance, Ciprofloxacin Intravenous Infusion BP). Starting materials for in situ API preparation should be treated as APIs in the Section 3.2.S of the application for registration. For example, in the case of Ciprofloxacin Intravenous Infusion BP, ciprofloxacin and lactic acid would be treated as APIs in the application for registration when they are used for the in situ preparation of ciprofloxacin lactate.

3.2. S.1.2 Structure (name, manufacturer)

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

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

3.2. S.1.3 General properties (name, manufacturer)

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

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

The physical and chemical properties of the API should be discussed including the physical description, solubility in common solvents (e.g. water, alcohols, dichloromethane, acetone); quantitative aqueous pH solubility profile (e.g. pH 1 to 6.8, dose/solubility volume); polymorphism; pH and pKa values; UV absorption maxima and molar absorptivity; melting point; refractive index (for a liquid); hygroscopicity; partition coefficient, etc. (see table in the QOS-PD). This list is not intended to be exhaustive, but provides an indication as to the type of information that could be included.

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

Physical description

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

Solubility/quantitative aqueous pH solubility profile

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

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

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

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

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

**Corresponding to the lowest solubility determined over the physiological pH range (pH1.2 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 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/1.0567 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 PD:

- the polymorphic form(s) present in the proposed API should be listed in Section 3.2.S.1.3;
- the description of the 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 documents: ICH 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 fabrication, packaging, labelling, testing and storage of the API should be listed. It should be clearly indicated, if certain companies are responsible only for specific steps (e.g. milling of the API).

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 authorisation (license) should be provided for the production of APIs. A certificate of GMP compliance in the format of a WHO-type GMP certificate from the competent authority of the country of manufacture should be provided in the PD in Module 1.

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

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

A flow diagram of the synthetic process(es) should be provided that includes molecular formulae, weights, yield ranges, chemical structures of starting materials, intermediates, reagents and API reflecting stereochemistry. The flow diagram should also identify operating conditions, purification steps, catalysts and solvents.

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

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

The <u>following requirements apply to the second option</u> for submission of API information, where full details are provided in the dossier.

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 justified by the manufacturer and accepted as such by assessors. This justification should be documented.

The *API starting material* should be fully characterised with respect to identity and purity. In addition, the steps prior to the step where the *API starting material* appears, which may involve *starting materials for synthesis*, should be available at least in the form of a flow chart. 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 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 the

maximum number of times that 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 crystallisation step[s]) should be clearly identified. Solvents used in the final steps should be of high purity. Use of recovered solvents in the final steps of purification and/or crystallization is not recommended.

Where 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) (e.g., 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 PMRA according to the requirements of the PMRA Guideline on Amendments.

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

Materials used in the manufacture of the API (e.g. raw materials, starting materials, solvents, reagents, catalysts) should be listed, identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials meet standards appropriate for their intended use should be provided, as appropriate (details in 3.2. A .2).

The following requirements apply to the second option for submission of API information, where full details are provided in the dossier.

In general, the starting material for synthesis described in the application for registration 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 characterised, 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 limits for assay and specified, unspecified and total impurities; and
- be incorporated as a significant structural fragment into the structure of the API.

For each starting material, the name and manufacturing site address of the manufacturer should be indicated. If there are several manufacturers, it should be clarified whether the starting material obtained from different sources is prepared by the same route of synthesis or if different routes are used. Specifications proposed for the starting material should apply to the material from each source.

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

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

For excipients obtained from sources that are at risk of transmitting Bovine Spongiform Encephalopathy (BSE)/Transmissible Spongiform Encephalopathy (TSE) agents (e.g., sources of ruminant origin), a letter of attestation (with supporting documentation) 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 documents: ICH 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.
Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.

The following requirements apply to the second option for submission of API information, where full details are provided in the dossier.

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

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

Reference documents: ICH 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.

The following requirements apply to the second option for submission of API information, where full details are provided in the dossier.

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 sterilisation 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)
A description and discussion should be provided of the significant changes made to the manufacturing process and/or manufacturing site of the API used in producing comparative bioavailability or biowaiver, scale-up, pilot, and, if available, production scale batches.

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

3.2. S.3 Characterization (name, manufacturer)

3.2. S.3.1 Elucidation of structure and other characteristics (name, manufacturer)
Confirmation of structure based on, e.g. synthetic route and spectral analyses should be provided. Information such as the potential for isomerism, the identification of stereochemistry, or the potential for forming polymorphs should also be included.

Elucidation of structure
The PD should include quality assurance (QA) certified copies of the spectra, peak assignments and a detailed interpretation of the data of the studies performed to elucidate and/or confirm the structure of the API. The PMRA 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 recognised 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 recognised pharmacopoeia, it is generally sufficient to provide copies of the IR spectra of the API from each of the proposed manufacturer(s), run concomitantly with a pharmacopeial reference standard. See Section 3.2.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 comparative bio-studies, and information should be given as to the stereoisomer of the API that is to be used in the FPP.

For non-pharmacopeial APIs, unequivocal proof of configuration of asymmetric centers such as x-ray of a single crystal should be provided when a single enantiomer of the API is claimed.

A discussion should be included of the possible isomers that can result from the manufacturing process, the steps where they were introduced or formed and a summary of the results of the studies carried out to investigate the physical, chemical and biological properties of these isomers. If there is a preferred isomer or isomeric mixture, a discussion of the material that was used in the comparative bioavailability or biowaiver study should be included and the API specification should include a test to ensure isomeric identity and purity.

If, based on the structure of the API, there is not a potential for isomerism, 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 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 crystallisation studies using different solvents and conditions.

There are a number of methods that can be used to characterise 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 characterise 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 characterisation of the API batches used in 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 lowdose 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 characterisation 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 documents: ICH Q6A

3.2. S.3.2 Impurities (name, manufacturer)

Information on impurities should be provided.

Details on the principles for the control of impurities (e.g. reporting, identification and qualification) are outlined in the ICH Q3A, Q3B and Q3C impurity guidelines. Additional information to provide further guidance on some of the elements discussed in the ICH guidelines is outlined below.

Regardless of whether a pharmacopeial 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 pharmacopeial APIs should not be limited to the impurities specified in the API monograph.

The tables in the QOS-PD template should be used to summarise the information on the APIrelated and process-related impurities. In the QOS-PD, 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 recognised 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 PD 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 recognised 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 FPP, acceptable to PMRA, 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 comparator 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/comparator.

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 summarise 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 pharmacopeial method to several recent batches to demonstrate the absence of the pharmacopoeia listed impurities.

ICH Class 2 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 guidance's (e.g. MEA/CHMP/QWP/251344/2006 or USFDA *Guidance for Industry: Genotoxic and carcinogenic impurities in drug substances and products, recommended approaches*, December 2008) 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 guideline on the specification limits for residues of metal catalysts or metal reagents EMEA/CHMP/SWP/4446/2000 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 recognised pharmacopoeias that cover metal contamination originating from manufacturing equipment and the environment.

Reference documents: ICH Q3A, Q3C, Q6A

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

3.2. S.4.1 Specification (name, manufacturer)

The specification for the API should be provided.

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 authorised personnel (e.g. the person in charge of the quality control or quality assurance department) should be provided in the PD, including specifications from each API manufacturer as well as those of the FPP manufacturer.

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

- The s*tandard* declared by the applicant could be an officially recognised compendial standard (e.g. Ph. Int. Ph. Eur., BP, USP) or a 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, 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 documents: ICH Q3A, Q3C, Q6A, *officially recognized pharmacopoeia (Ph. Int, BP, USP, Ph. Eur.)*

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

The analytical procedures used for testing the API should be provided.

Copies of the in-house analytical procedures used to generate testing results provided in the PD, as well as those proposed for routine testing of the API by the FPP manufacturer should be provided. Unless modified, it is not necessary to provide copies of officially recognized compendia 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 PMRA-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 PMRA-QOS. Other methods used to generate assay and purity data in the PD can be summarised in 2.3.S.4.4 (c) or 2.3.S.7.3 (b) of the PMRA-QOS. Officially recognised compendia methods need not be summarised 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 documents: ICH Q2, 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 API, should be provided.

Copies of the validation reports for the analytical procedures used to generate testing results provided in the application file, 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 PMRA 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 QOSPD. The validation data for other methods used to generate assay and purity data in the PD can be summarized in 2.3.S.4.4 (c) or 2.3.S.7.3 (b) of the PMRA QOS.

As recognised 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 recognised compendial method is used to control API-related impurities that are not specified in the monograph, full validation of the method is expected with respect to those impurities.

If an officially recognised compendial standard is claimed and an in-house method is used in lieu of the compendial method (e.g. for assay or for specified impurities), equivalency of the in-house and compendial methods should be demonstrated. This could be accomplished by performing duplicate analyses of one sample by both methods and providing the results from the study. For impurity methods, the sample analysed should be the API spiked with impurities at concentrations equivalent to their specification limits.

Reference documents: ICH Q2

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

Description of batches and results of batch analyses should be provided.
The information provided should include batch number, batch size, date and production site of relevant API batches used in comparative bioavailability or biowaiver studies, 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 summarised in the PMRA-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 documents: ICH Q3A, Q3C, Q6A

3.2. S.4.5 Justification of specification (name, manufacturer) **Justification for the API specification should be provided.**

A discussion should be provided on the inclusion of certain tests, evolution of tests, analytical procedures and acceptance criteria, differences from the officially recognised compendial standard(s), etc. If the officially recognised 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 file (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 documents: ICH Q3A, Q3C, Q6A, *officially recognised pharmacopoeia*

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

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

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

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

A suitable primary reference standard should be obtained from an officially recognised pharmacopeial source (e.g. Ph. Int, Ph. Eur, BP, and USP) 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 recognised pharmacopeial sources do not need further structural elucidation.

Otherwise, a primary standard may be a batch of the API that has been fully characterised (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 characterised 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 documents: ICH Q6A, WHO Technical Report Series, No. 943, Annex 3

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.

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

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

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

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

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

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 summarised. 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 shelflife, as appropriate.

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 PMRA-QOS template should be used to summarise 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 WHO Technical Report Series, No. 953, Annex 2, Section 2.1.2, as well as, "A typical set of studies of the degradation 1379 paths of an active pharmaceutical ingredient" 1380 in WHO Technical Report Series, No. 929, Annex 5, Table A.1.

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 nondegraded 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 PMRA QOS template should be used to summarise 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 recognised 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 by PMRA is either 30ºC±2ºC/65%±5%RH or 30ºC±2ºC/75%±5%RH. Studies covering the proposed retest period at the above-mentioned long-term storage conditions will provide better assurance of the stability of APIs at the conditions of the supply chain corresponding to the Malawian environment. Alternative conditions should be supported with appropriate evidence, which may include literature references or in-house studies, demonstrating that storage at 30ºC is inappropriate for the API. For APIs intended for storage in a refrigerator and those intended for storage in a freezer refer to the WHO stability guideline WHO Technical Report Series, No. 953 Annex 2. APIs intended for storage below -20°C should be treated on a case-by-case basis.

To establish the retest period, data should be provided on not less than three batches of at least pilot scale. The batches should be manufactured by the same synthesis route as production batches and using a method of manufacture and 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-PD.

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) are as follows:

	Storage temperature(ºC)	**Relative humidity (%)**	**Minimum time period (months)**
1. Accelerated	40±2	75±5	6
2. Intermediate *	-	-	-
3. Long-term	30±2	65±5 or 75±5	6

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

Refer to WHO Technical Report Series, No. 953, Annex 2 for further information regarding the storage conditions, container closure system, test specifications and testing frequency.

Proposed storage statement and retest 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 retest period should be derived from the stability information and should be displayed on the container label.

After this retest period, a batch of API destined for use in the manufacture of an FPP could be retested and then, if in compliance with the specification, could be used immediately (e.g. within 30 days). If retested and found compliant, the batch does *not* receive an additional period corresponding to the time established for the retest period. However, an API batch can be retested multiple times and a different portion of the batch used after each retest, 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 shelflife rather than a retest period (reference: ICH Q1A).

Limited extrapolation of the real time data from the long-term storage condition beyond the observed range to extend the retest period can be undertaken at the time of assessment of the PD, 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 retest 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 documents: ICH Q1A, Q1B, Q1D, Q1E, WHO Technical Report Series, No. 953, Annex 2

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 retest period granted at the time of assessment of the application file, a commitment should be made to continue the stability studies in order to firmly establish the retest period. A written commitment (signed and dated) to continue long-term testing over the retest 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 retest 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:

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

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 retest 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 WHO Technical Report Series, No. 953, Annex 2, Section 2.1.11 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 documents: ICH Q1A, Q1B, Q1D, Q1E, WHO Technical Report Series, No. 953, Annex 2

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 retest 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 documents: ICH Q1A, Q1B, Q1D, Q1E, Q2, WHO Technical Report Series, No. 953, Annex 2.

3.2. P Drug product (or 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 summarise 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, House) and, if applicable, their grades (e.g. "Microcrystalline Cellulose NF [PH 102]") and special technical characteristics (e.g. lyophilised, micronised, 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 diluent(s)**

For FPPs supplied with reconstitution diluent(s) that are commercially available or have been assessed and considered acceptable for this purpose, 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 by PMRA, 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 foils unit dose blisters (in packages of 100's (cards of 5 x 2, 10 cards per package)."

Reference documents: ICH 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 product dossier. The studies described here are distinguished from routine control tests conducted according to specifications. Additionally, this section should identify and describe the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance and FPP quality. Supportive data and results from specific studies or published literature can be included within or attached to the Pharmaceutical Development section. Additional supportive data can be referenced to the relevant non-clinical or clinical sections of the product dossier.

Pharmaceutical development information should include, at a minimum:

a) the definition of the quality target product profile (QTPP) as it relates to quality, safety and efficacy, considering for example the route of administration, dosage form, bioavailability, strength and stability;

b) identification of the potential critical quality attributes (CQAs) of the FPP so as to adequately control the product characteristics that could have an impact on quality;

c) discussion of the potential CQAs of the API(s), excipients and container closure system(s) including the selection of the type, grade and amount to deliver drug product of the desired quality;

d) discussion of the selection criteria for the manufacturing process and the control strategy required.

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).

In case of fixed-dose combination FPPs, the development strategy should take into account the formulae of the individual component comparator FPPs. The compatibility of APIs with each other should be studied and the results documented. 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 documents: ICH Q6A, Q8, Q9 and Q10.

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

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

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

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

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 FPP performance should be discussed relative to their respective functions.

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 Finished pharmaceutical product (name, dosage form)

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

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

PMRA defines an *established multisource 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 multisource product,* all sections of P.2.2.1 of the dossier and QOS-PD should be completed with the exception of P.2.2.1 (a). In addition, a product quality review should be provided as outlined in Annex V.

Break-marks (score lines) are justified in the tablets only when the tablet can be divided into fractional doses according to approved posology or is specified for the FPP in the listing of recommended comparator products.

If the proposed FPP is a scored tablet, it should comply with the requirements of the Ph. Eur. (Subdivision of tablets test) and the results of the study of the uniformity of dosage units of the tablet halves should be provided. The data provided in the PD should include a description of the test method, individual values, mean and relative standard deviation (RSD) of the results. Uniformity testing (i.e. content uniformity or weight variation, depending on the requirement for the whole tablet) should be performed on each split portion from a minimum of 10 randomly selected whole tablets. 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 eachstrength 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 insert) should reflect the presence of a score.

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 Annexure VI.

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 generally not acceptable.

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

Parameters relevant to the performance of the FPP, 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.

In addition to the above considerations, refractive index may be a relevant parameter for some FPPs.

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

The selection and optimisation of the manufacturing process described in 3.2.P.3.3, in particular its critical aspects, should be explained. Where relevant, the method of sterilisation should be explained and justified.

Where relevant, justification for the selection of aseptic processing or other sterilisation methods over terminal sterilisation should be provided.

Differences between the manufacturing process (es) used to produce comparative bioavailability or biowaiver 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-PD should be completed and a product quality review should be submitted as outlined in Annexure V. 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 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, optimisation 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, mixing time, granulation end-point). The equipment should be identified by type and working capacity.

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 FPP should be discussed. This discussion should consider, e.g. choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching) safety of materials of construction, and performance (such as reproducibility of the dose delivery from the device when presented as part of the FPP).

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 onetime studies to establish the suitability of the container closure system.

Table 2: Demonstration of suitability of container closure system

	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, siliconisation of rubber stoppers, sulfur 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 multi-dose 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 multi-dose 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 in *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 WHO stability guideline (WHO Technical Report Series, No. 953, Annex 2, 2009), 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 FPP with reconstitution diluent(s) or dosage devices (e.g. precipitation of API in solution, sorption on injection vessels, stability) should be addressed to provide appropriate and supportive information for the labelling.

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

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

Studies should cover the duration of storage reported in the labelling (e.g. 24 hours under controlled room temperature and 72 hours under refrigeration). Where the labelling specifies coadministration 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 fabrication, packaging, labelling and testing should be listed. It should be clearly indicated if certain companies are responsible only for specific steps (e.g. manufacturing of an intermediate). (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 authorisation for pharmaceutical production, as well as a marketing authorisation, should be submitted to demonstrate that the product is registered or licensed in accordance with national requirements in the country of origin or country of manufacture (*Module 1*, 1.2.2).

For each site where the major production step(s) are carried out, when applicable, attach a WHOtype certificate of GMP issued by 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 authorisation, 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. 908, Annex 4 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.

Table 3 below should be used to summarise 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.

Table 3: Batch formula

Strength (label claim)			

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

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, House) and, if applicable, their grades (e.g. "Microcrystalline Cellulose NF [PH 102]") and special technical characteristics (e.g. lyophilised, 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 presents 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 bulk FPP prior to final packaging should be stated. The holding time should be supported by the submission of stability data, if longer than 30 days. For an aseptically processed FPP, sterile filtration of the bulk and filling into final containers should preferably be continuous; any holding time should be justified.

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

The information above should be summarised in the QOS-PD template and should reflect the production of the proposed commercial batches. See Section *2. Glossary* for definitions of pilotscale and production-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 sterilisation parameters for equipment, container/closure, terminal sterilisation etc.

Reference documents: ICH 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, bulk and tapped
- densities, particle size distribution;

- solid oral products: average weight, weight variation, hardness, thickness, friability,
- disintegration, weight gain during coating;
- fixed-dose combinations (FDCs): uniformity of content of each active prior to compression (tablets) or filling (e.g. capsules, sachets and suspension dosage forms);
- 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.

Reference documents: ICH 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 sterilisation process or aseptic processing or filling). Viral safety evaluation should be provided in 3.2A.2, if necessary.

For products that meet the criteria of an *established multisource product*, a product quality review as outlined in Annexure V 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, that identifies the critical equipment and process parameters that can affect the quality of the FPP and defines testing parameters, sampling plans, analytical procedures and acceptance criteria;
b) a *commitment* that three consecutive, production-scale batches of this FPP will be subjected to *prospective validation* in accordance with the above protocol;
c) The applicant should submit a written commitment that information from these studies will be available for verification after the FPP is registered by PMRA and,
d) if the process validation studies have already been conducted (e.g. for sterile products), a copy of the *process validation report* should be provided in the PD in lieu of (a) and (b) above.

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. Products (intermediate or final) may occasionally be tested for non-routine characteristics. Thus, sub visual particulate matter in parenteral preparations may be determined by means of electronic devices, or tablets/capsules tested for dissolution profile if such tests are not performed on every batch.

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 testing of the final blend);
- the testing parameters/acceptance criteria including in-process and release specifications;
- the analytical procedures or a reference to appropriate section(s) of the dossier; − the methods for recording/evaluating results; and
- the proposed timeframe for completion of the protocol.

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

a) washing, treatment, sterilising and depyrogenating of containers, closures and equipment; b) filtration of solutions;
c) lyophilisation process;
d) leaker test of filled and sealed ampoules;
e) final inspection of the product; and
f) sterilisation cycle.

The sterilisation 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 sterilisation (e.g. ethylene oxide), or radiation. It should be noted that terminal steam sterilisation, 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 sterilisation should be provided.

The sterilisation 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 Fo 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 filling of parenteral products that cannot be terminally sterilised, simulation process trials should be conducted. This involves filling ampoules with culture media under normal conditions, followed by incubation and control of microbial growth. A level of contamination of less than 0.1% is considered to be acceptable.

Reference documents: ICH Q8, Q9, Q10, WHO Technical Report Series, Nos. 902 and 908

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 recognised 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 recognised 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 recognised compendial monograph, a copy of the specification for the excipient should be provided.

For products submitted for registration, only excipients with an officially recognised pharmacopeial monograph should be used. Exceptions should be 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"[1], the EU "List of permitted food colours"[2], and the FDA "Inactive ingredient guide"[3]. 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).

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[1] Japanese pharmaceutical excipients. Tokyo, Pharmaceutical and Cosmetics Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare (updated annually or biennially).

[2] List of permitted food colors, Official journal of the European Communities, 1994. L237. (European Commission Directive 94/36/EC).

[3] Inactive ingredient guide. Rockville, MD, United States Food and Drug Administration, Division of Drug Information and Research, 1996.

Information that is considered confidential may be submitted directly to the PMRA by the supplier with reference to the specific related product.

Annexure VII contains ingredients which PMRA has gazetted as undesirable in pharmaceutical preparations. Any applications containing such ingredients will be rejected.

The use of alcohol in oral pharmaceutical formulation is generally discouraged. The Authority has set the limits of alcohol content oral pharmaceutical products at NMT 10% for adult preparations and NMT 5% in paediatric preparations.

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 documents: ICH Q6A

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 recognised compendial monographs do not need to be submitted. Non-compendial analytical procedures used for testing the excipients should be provided, where appropriate.

Reference documents: ICH 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 normally not submitted for the testing of excipients, with the exception of the validation of in-house methods where appropriate.

Reference documents: ICH 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 recognised 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, and viral safety data) (details in 3.2.A.2).

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

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

Materials of animal origin should be avoided whenever possible.

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

Reference documents: ICH Q5A, Q5D, Q6B, WHO Technical Report Series, No. 908, Annex 1

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

For excipient(s) used for the first time in an FPP or by a new route of administration, full details of manufacture, characterisation, and controls, with cross references to supporting safety data (non-clinical and/or clinical) should be provided according to the API and/or FPP format (details in 3.2.A.3).
Novel excipients are generally not recommended in products submitted for registration unless adequate justification is provided. 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 an SRA or WHO.

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

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

The specification(s) for the FPP should be provided.

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."

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 authorised personnel (i.e. the person in charge of the quality control or quality assurance department) should be provided in the PD. Two separate sets of specifications may be set out: after packaging of the FPP (release) and at the end of shelf-life.

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

- the *standard* declared by the applicant could be an officially recognised compendial standard (e.g. Ph. Int., BP, USP) or a 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), the *source* refers to the origin of the analytical procedure (e.g. Ph. Int., Ph. Eur., BP, USP, 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, pharmaceutical tests (e.g. dissolution), physical tests (e.g. loss on drying, hardness, friability, particle size, apparent density), uniformity of dosage units, identification of colouring

materials, 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:

- For 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 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,
  - when any one API is present at less than 25 mg or less than 25% of the weight of the dosage unit, a test and limit for content uniformity is required for each API in the FPP,
  - when all APIs are present at greater than 25 mg and greater than 25% of the weight of the dosage unit, a test and limit for weight variation may be established for each API in the FPP, 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 *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: NLT every tenth batch and at least one batch annually is tested. In addition, for stability-indicating parameters such as microbial limits, assay and degradants, 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 documents: ICH Q3B, Q3C, Q6A

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

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

Tables for summarising 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 PMRA QOS (i.e. *2.3.R.2)*. These tables should be used to summarise 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 documents: ICH 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 FPP, should be provided.

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

Tables for summarising 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-PD (i.e. *2.3.R.2)*. These tables should be used to summarise the validation

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

As recognised 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 recognised compendial FPP *assay* methods, verification should include a demonstration of specificity, accuracy and repeatability (method precision). If an officially recognised 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 recognised compendial standard is claimed and an in-house method is used in lieu of the compendial method (e.g. for assay or for related compounds), equivalency of the in-house and compendial methods should be demonstrated. This could be accomplished by performing duplicate analyses of one sample by both methods and providing the results from the study. For related compound methods, the sample analysed should be the FPP spiked with related compounds at concentrations equivalent to their specification limits.

Reference documents: ICH 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, 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[4] (e.g.

[4] The term "complicated FPP" includes sterile products, metered dose inhaler products, dry powder inhaler products and transdermal delivery systems. Other specific products under "complicated FPP" include ritonavir/lopinavir FDC tablets and FDCs containing rifampicin or an artemisinin.

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 PD 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 documents: ICH Q3B, Q3C, Q6A

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

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

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

Reference documents: ICH Q3B, Q3C, Q6A

Due to the rolling nature of the products listed in the invitations for EOI, the listing of individual "complicated" FPPs is not meaningful and applicants should contact PMRA in case of doubt.

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

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

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

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

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

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

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

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

Reference documents: ICH 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 recognised 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 conclusions (name, dosage form)

The types of studies conducted, protocols used, and the results of the studies should be summarised. 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 WHO stability guideline *Stability testing of active pharmaceutical ingredients and finished pharmaceutical products* (WHO Technical Report Series, No. 953, Annex 2, 2009) should be

consulted for recommendations on the core stability data package required for the registration of products.

As outlined in the WHO 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 program 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 WHO 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 recognised 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 shelflife under the climatic conditions for Climatic Zone IV.

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

	Storage temperature (ºC)	**Relative humidity (%)**	**Minimum time period (months)**
Accelerated	40±2	75±5	6
Intermediate *	N/A	N/A	
Long-term	30±2	65±5**	12

*Where long-term conditions are 30ºC±2ºC/75%±5%RH, there is no intermediate condition.
** Stability studies conducted at 75% relative humidity are also acceptable

Other storage conditions are outlined in the WHO stability guideline for FPPs packaged in impermeable and semi-permeable containers and those intended for storage in a refrigerator and in a freezer. FPPs intended for storage below -20°C should be treated on a case-by-case basis.

To establish the shelf-life, data should be provided on 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 stability testing programme should be summarised and the results of stability testing should be reported in the dossier and summarised using the tables below. Bracketing and matrixing of proportional strengths can be applied, if scientifically justified.

Table 4: Summary of accelerated and long-term testing parameters (e.g. studies conducted

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

Table 5: Summary of the accelerated and long term stability results

Test	Results
Description	
Moisture	
Impurities	
Assay	
etc.	

Copies of certificates of analysis at the start of stability studies should be submitted.

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. In-use periods for parenteral and ophthalmic products should be justified with experimental data.

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.

Table 6: Proposed shelf life and storage conditions

Container closure system	Storage statement	Shelf-life

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

Reference documents: WHO Technical Report Series, No. 953, Annex 2, ICH Q1A, Q1B, Q1C, Q1D, Q1E, Q3B, 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 product 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

As described in the WHO stability guideline, 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 for each 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 documents: ICH 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, and 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 product 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 documents: ICH Q1A, Q1B, Q1C, Q1D, Q1E, Q2

3.2. A Appendices

3.2. A.1 Facilities and equipment

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

3.2. A.2 Adventitious agents safety evaluation

3.2. A.3 Novel excipients

3.2. R Regional information

3.2. R.1 Production documentation

3.2. R.1.1 Executed production documents

A minimum of two batches of at least pilot scale, or in the case of an uncomplicated FPP (e.g. immediate-release solid FPPs (with noted exceptions), non-sterile solutions), not less than one batch of at least pilot scale (the batch used in comparative bioavailability or biowaiver studies) and a second batch which may be smaller (e.g. for solid oral dosage forms, 25 000 or 50 000 tablets or capsules), should be manufactured for each strength. These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

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

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

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

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

English translations of executed records should be provided, where relevant.

Alternatively in cases where BMR cannot be submitted i.e. for innovator products, the following should be submitted:

- A formal communication (written correspondence) from the applicant of the innovator company seeking exemption from submission of batch records giving reasons thereof
- A WHO-type Certificate of Pharmaceutical product (CPP) issued by one of the regulatory authorities of the ICH region or associated countries
- A summary of product characteristics (SmPC) approved by the respective regulatory authority
- A copy of the quality assessment report issued by a competent regulatory authority. This may be send directly from the drug regulatory authority in the country of origin of the product to the PMRA
- A WHO-type batch certificate from the manufacturer
- An undertaking that the packaging of the product is the same as that approved by the drug regulatory authorities of the ICH region and associated countries
- The product information to be the same as on the WHO-type CPP for at least unit and batch composition, strength and specifications

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, Nos. 902 and No. 908

3.2. R.2 Analytical procedures and validation information

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

3.3 Literature references

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

MODULE 5 OF A PRODUCT DOSSIER FOR A MULTISOURCE PHARMACEUTICAL PRODUCT

The majority of product dossiers for multisource products are supported by one or more pivotal comparative bioavailability studies. When filing a product dossier in the CTD format, it is anticipated that only the following relevant sections of Module 5 will normally be required.

Module 5: Clinical study reports

5.1 Table of contents for Module 5
5.2 Tabular listing of all clinical studies
5.3 Clinical study reports
5.3.1 Reports of biopharmaceutical studies
5.3.1.2 Comparative bioavailability and bioequivalence study reports
5.3.1.3 In vitro-in vivo correlation study reports
5.3.1.4 Reports of bioanalytical and analytical method for human studies
5.3.7 Case report forms and individual patient listings
5.4 Literature references

For guidance regarding biowaivers, refer to the biowaiver implementation documents available on the PMRA website. For guidance regarding comparator products, refer to the information available under Guidance on Bioequivalence Studies on the PMRA website.

REFERENCES

1. Guidelines on packaging for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report.* Geneva, World Health Organization, 2002, Annex 9 (WHO Technical Report Series, No. 902)

2. Good manufacturing practices for sterile pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report.* Geneva, World Health Organization, 2002, Annex 6 (WHO Technical Report Series, No. 902)

3. Good manufacturing practices for pharmaceutical products: main principles. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report.* Geneva, World Health Organization, 2003, Annex 4 (WHO Technical Report Series, No. 908)

4. Recommendations on risk of transmitting animal spongiform encephalopathy agents via medicinal products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report.* Geneva, World Health Organization, 2003, Annex 1 (WHO Technical Report Series, No. 908)

5. Guidelines for registration of fixed-dose combination medicinal products. Appendix 3: Pharmaceutical development (or preformulation) studies. Table A1: Typical stress conditions in preformulation stability studies. In: *WHO Expert Committee on Specifications for*

Pharmaceutical Preparations. Thirty-ninth report. Geneva, World Health Organization, 2005, Annex 5 (WHO Technical Report Series, No. 929).

6. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: *WHO Expert Committee on Specifications for Pharmaceutical*

Preparations. Fortieth report. Geneva, World Health Organization, 2006, Annex 7 (WHO Technical Report Series, No. 937)

7. General guidelines for the establishment, maintenance and distribution of chemical reference substances. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first report.* Geneva, World Health Organization, 2007, Annex 3 (WHO Technical Report Series, No. 943).

8. Guidelines on active pharmaceutical ingredient master file procedure. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-second report.* Geneva, World Health Organization, 2008, Annex 4 (WHO Technical Report Series, No. 948).

9. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-third report.* Geneva, World Health Organization, 2009, Annex 2 (WHO Technical Report Series, No. 953)

10. Procedure for prequalification of pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-third report.* Geneva, World Health Organization, 2009, Annex 3 (WHO Technical Report Series, No. 953)

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

ANNEX I: FORM 8A

FORM 8A

Quality Medicines for Malawi

The Pharmacy and Medicines Regulatory Authority Act, 2019
(Act No. 9 of 2019, Part IV Section 62)

APPLICATION FOR A MARKETING AUTHORISATION			
Please complete it electronically	Shaded fields for official use only	Application No.	
		Date and Time	
Information required	*Information Provided*		
PART 1 **PARTICULARS OF APPLICANT**			

A	**PARTICULARS OF COMPANY**		
1.	(a) Name of business entity		
	(b) Tax Payer Identification Number (where applicable)		
2.	Type of business entity		
3.	Business premises		
	a) Plot No:		
	b) Street:		
	c)Telephone No:		
	d) Fax No:		
	e) Mobile No:		
	f) Email address		
	g) Postal address		
	h) Town		
	i) District		
	j) Province		
	k) Country		
B	**CONTACT PERSON**		
	a) Name		
	b) Designation		
	c)Physical address		
	d) Postal address		
	e) Phone No.		
	f) Fax No.		
	g) Email address		
C	**LOCAL RESPONSIBLE PERSON (Applicable to foreign based applicants)**		
	Name		
	Designation		
	Physical address		
	Postal address		
	Phone No.		
	Fax No.		

	Email address		
PART II **PARTICULARS OF THE PRODUCT**			
1.	Name of the medicine		
2.	International non-proprietary names of the active pharmaceutical ingredient, including form (salt, hydrate, polymorph) and strength (in case of a herbal medicine, specify the botanical, English or any other name and the quantities of each ingredient)		
3.	ATC code		
4.	Dosage form		
5.	Route of administration		
6.	Name and site address of source of the active raw material (in case of herbal medicine)		
7.	Container, closure and administration system		
8.	Proposed indication (specify target species in case of veterinary medicine)		
9.	Package size		
10	Shelf life (months)		
11	Storage conditions/ instructions		
12	Proposed category of distribution		
13	Marketing authorisation status in other countries		

	PART III **PARTICULARS OF MANUFACTURER**						
	Name, address and responsibility (e.g. fabrication, packaging, labelling, testing etc.) of each manufacturer, including contractors and each proposed production site or facility involved in manufacturing and testing of the product:						
1.	Name:						
2.	Physical address (include block(s)/unit(s) if applicable						
3.	Responsibility:						
	If more than one site is involved (e.g. manufacturing of dosage form, primary packaging, release etc.), clearly identify the site for each stage.						
	Copies of the latest GMP certificate for manufacturer and packers or a copy of the appropriate manufacturing licence issued by Pharmacy and Medicines Regulatory Authority or any PICs country.						
	Declaration letter stating that any subsequent inspection did not reveal non-conformance to GMP requirements.						
	PART IV **COMPOSITION**						
	List of all components of the finished pharmaceutical product and their amounts on a per unit, batch and percentage basis including individual components of mixtures prepared in-house (e.g. coatings) and overages, if any						
	Ingredients and quality standard (in case of a herbal medicine,	**Function (reason for inclusion)**	**Strength (Label Claim)**				
			Quantity per unit dosage form (e.g. mg/Tablet)	**% per unit dosage form**	**Quantity per batch**	**% per batch**	

	specify the botanical, English or any other name						
	<complete with appropriate title e.g. core tablet, contents of capsule, powder for injection>						
	Subtotal 1						
	<complete with appropriate title e.g. film-coating>						
	Subtotal 2						
	Total						

PART V
PROPOSED SCHEDULE

	Controlled Drug (CD)		POM		PIM		P		GSL	

Applicants are encouraged to indicate which category they are requesting, however, Pharmacy and Medicines Regulatory Authority reserves the right to change and/or apply only those categories provided for in their legislation.

PART VI
EVIDENCE OF REGISTRATION

State whether the product is registered in originating country (attach evidence of registration in the form of Certificate of Pharmaceutical Product (COPP) from National Medicines Regulatory Authority).

List ICH and/or Observers where the product is approved (attach evidence of registration)

State whether the product has been withdrawn/suspended/revoked in any regulated market

	Date of		Reason for	

	withdraw/suspension /revocation		withdraw/suspension/revocation		

PART VII
TYPE OF APPLICATION

Indicate the type of medicine, the type of data included as proof of efficacy, and the review procedure using a check mark (√) or a cross (X)

Human Medicine:		NCE		**Data as proof of efficacy:**	
Chemical		Multisource		Preclinical	
Biological		Biosimilar		Clinical	
Veterinary Medicine:				Bio-study	
Chemical				BCS biowaiver	
Biological				Bibliography	
Herbal:					

Review Procedure proposed by the applicant:

Routine		WHO CRP/SRA		ZAZIBONA		Fast Track (Expedited)	

DECLARATION AND SIGNATURE:

I declare that all the information I have stated in this application is correct and truthful to the best of my knowledge and belief. I understand that submission of false information shall render the application void and that if approval is granted, the market authorisation may be revoked.

Particulars of the Person signing on behalf of the Applicant

…… ……..

Name Designation

……	……
Signature	Date

FOR OFFICIAL USE ONLY

Date of Submission:
……

Application Number:
……

Payments Receipt Number:
……

Application complete (proceed to evaluation):
……

Application incomplete (refer to applicant for additional information):
……

……
……

OFFICIAL
STAMP

ANNEX II: SCREENING CHECKLIST

SECTION		DOCUMENTS	Submitted?		
			Yes	No	Location (Page numbers)
1.		ADMINISTRATIVE INFORMATION			
	1.1	Comprehensive Table of Contents **~Include a complete list of all documents provided in the product dossier by module** **~The location of each document should be located by the module number**			

	1.2	Completed, signed and dated FORM 8A form			
	1.3	Introduction			
		~ Quality Information Summary			
		~Justification for the lack of certain documents and deviation(s) from guidelines			
	1.4	Labelling			
	1.4.1	Copies of Outer carton Labels			
	1.4.2	Copies of Inner/Blister Labels			
	1.4.3	Copies of Package Insert (PI)			
	1.4.4	Copies of Patient Information Leaflet (PIL)			

	1.5	SmPC for Innovator Product			
	1.6	GMP certification/proof of GMP compliance for each FPP manufacturer {inclusive of secondary packer(s)} from a competent authority			
		GMP certification/proof of GMP compliance for each active pharmaceutical ingredient (API) manufacturer			
2.		COMMON TECHNICAL DOCUMENT SUMMARIES			
	2.1	**Overall CTD Table of Contents of Modules 2, 3, 4 and 5**			

	2.2	**Introduction**			
	2.3	Quality Overall Summary (QOS)			
	2.4	Non-clinical Overview			
	2.5	Clinical Overview			
	2.6	Non-clinical Summary			
	2.6.1	**Introduction**			
	2.6.2	**Pharmacology Written Summary**			
	2.6.3	**Pharmacology Tabulated Summary**			
	2.6.4	**Pharmacokinetics Written Summary**			
	2.6.5	**Pharmacokinetics Tabulated Summary**			
	2.6.6	**Toxicology Written Summary**			
	2.6.7	**Toxicology Tabulated Summary**			

	2.7	Clinical Summary			
	2.7.1	**Summary of Biopharmaceutics and Associated Analytical Methods**			
	2.7.2	**Summary of Clinical Pharmacology Studies**			
	2.7.3	**Summary of Clinical Efficacy**			
	2.7.4	**Summary of Clinical Safety**			
	2.7.5	**Synopses of Individual Studies**			
3.		QUALITY			
	3.1	Module 3 Table of Contents			

	3.2	**Body of Data**		
3.2.S		ACTIVE PHARMACEUTICAL INGREDIENTS		
		~If CEP (Certificate of Suitability) is submitted, **waiver of documents for this section can be granted except for S4.1, S4.2 & S4.4.** **~Please note that information not included in the CEP** **would have to be supported by substantial data (e.g.** **S6 & S7 is required if no retest period and/or packaging is stated in the CoA).**		
		Certificate of suitability (CEP)		
3.2.S.2.1		Manufacturer(s) name and address		
3.2.S.2.2		Description of Manufacturing Process and Process Controls		
3.2.S.2.3		Control of Materials		*
3.2.S.2.4		Controls of Critical Steps and Intermediates		*
3.2.S.2.5		Process Validation and/or Evaluation **~ Must be submitted for sterile APIs and NCEs**		*
3.2.S.2.6		Manufacturing Process Development		*

***: For applications with DMF, sections S2.3, S2.4, S2.5 and S2.6 are included in the closed part of DMF**				
3.2.S.3	CHARACTERISATION			
3.2.S.3.1	**Elucidation of Structure and other Characteristics**			
3.2.S.3.2	**Impurities**			
3.2.S.4	CONTROL OF API			
3.2.S.4.1	Specifications of API			
3.2.S.4.2	Analytical Procedures			
3.2.S.4.3	Validation of Analytical Procedures ***: Can be waived for methods that reference compendial methods**			*
3.2.S.4.4	Batch Analyses for three batches			
3.2.S.4.5	Justification of Specification ***: Justification is not required if compendial requirements are met**			*
3.2.S.5	REFERENCE STANDARDS			
3.2.S.6	CONTAINER CLOSURE SYSTEM			
	Specifications			
	Test Methods			
3.2.S.7	STABILITY			
3.2.S.7.1	Stability Summary and Conclusions			

3.2.S.7.2		Post-approval Stability Protocol and Stability Commitment			
3.2.S.7.3		Stability Data **~ At point of submission, at least 12 months of real time data and 6 months of accelerated data on at least 3 primary batches of the API should be provided**			
		Forced Degradation studies			
		Accelerated Stability Studies			
		Real-Time Stability Studies			
		NOTE: S6 & S7 would have to be submitted if the retest period is not stated in the CEP			
3.2.P		FINISHED PHARMACEUTICAL PRODUCT (FPP)			
3.2.P.1		Description and Composition of the FPP			
3.2.P.2		Pharmaceutical Development			
3.2.P.3		Manufacture			
	3.1	Manufactuer(s) name(s) and physical address(es)			
	3.2	Batch Formula **~For multiple batch sizes, batch formula for each batch sizes are to be provided**			
	3.3	Description of manufacturing process and process controls			
	3.4	Control of critical steps and intermediates			

	3.5	Process validation **~For three consecutive batches**			
3.2.P.4		Control of Excipients			
	4.1	Specifications			
	4.2	Analytical Procedures			
	4.3	Validation of Analytical Procedures			
	4.4	Justification of Specifications			
	4.5	Excipients of Human or Animal Origin ***: BSE / TSE free certification**			*
	4.6	Novel excipients *: **Provide information provided as per full API Section**			*
3.2.P.5		Control of FPP			
	5.1	Specification(s) of Finished Pharmaceutical Product (FPP)			
	5.2	Analytical Procedures			
	5.3	Validation of Analytical Procedures			
	5.4	Batch Analyses for two batches			
	5.5	Characterisation of Impurities			
	5.6	Justification of Specification(s)			
3.2.P.6		Reference Standards			
3.2.P.7		Container- Closure System			

		Test Methods			

		Specifications			
3.2.P.8		Stability			
	8.1	Stability Summary and Conclusions			
	8.2	Post-approval Stability Protocol and Stability Commitment			*
	8.3	Stability Data **~accelerated for 6 months for two batches** **~real time for at least 6 months for two batches *: (at time of approval at least 12 months real time stability data should have been provided)**			
		Photostability Data			
		Accelerated Stability Data			
		Real-time Stability Data			
3.2.R		REGIONAL INFORMATION/ REQUIREMENTS			
3.2.R.1		Production documentation			*
		Executed production documents **Master production documents**			
3.2.R.2		Analytical procedures and validation information			*
3.3		LITERATURE REFERENCES			*
4		NON-CLINICAL STUDY REPORTS			

	4.1	**Table of Contents**			
	4.2	Study Reports			
	4.2.1	Pharmacology			
	4.2.2	Pharmacokinetics			
	4.2.3	Toxicology			
	4.3	List of Literature References			
5		CLINICAL STUDY REPORTS			
	5.1	**Module 5 Table of Contents**			
	5.2	Tabular Listing			
	5.3	Clinical Study Reports			
	5.3.1	Reports of Biopharmaceutical Studies			
	5.3.2	Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials			
	5.3.3	Reports of Pharmacokinetic (PK) Studies			
	5.3.4	Reports of Pharmacodynamic (PD) Studies			
	5.3.5	Reports of Efficacy and Safety Studies **~ Study reports of ALL clinical trials, including the appendices & tables** **~ Study reports of pivotal or relevant clinical trials**			
	5.3.6	Reports of Post-marketing Experience			
	5.3.7	Case Report Forms and Individual Patient Listings			
	5.4	**List of Key Literature References**			

	5.5	**Other Supporting Documents**	

ANNEX III: SMPC/ Package Insert

Structure of the package insert
(with proposed sentence patterns and illustrative examples)

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

{(Trade/Invented) name of product <strength> <pharmaceutical form>}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

For excipients, see 6.1.

3. PHARMACEUTICAL FORM 4. CLINICAL PARTICULARS

4.1 Therapeutic indications

<xxx is indicated for use in uncomplicated malaria. >

4.2 Posology and method of administration

Adults (for example)
Children and adolescents (4 to 17 years of age) (for example)
General administration recommendations (for example) Special dosing considerations in adults (for example)

4.3 Contraindications

<Hypersensitivity to the API(s) or to any of the excipients <or {residues }>.

4.4 Special warnings and special precautions for use

Drug interactions (for example)
Acute haemolytic anaemia (for example)
Hyperglycaemia (for example)
Patients with coexisting conditions (for example) Other

4.5 Interaction with other FPPs and other forms of interaction

Rifabutin (for example)
Ketoconazole (for example)
Itraconazole (for example)
Nevirapine (for example)
HMG -CoA reductase inhibitors (for example)
Rifampicin (for example) Other

4.6 Pregnancy and lactation

Use during pregnancy (for example) Use
during lactation (for example)

4.7 Effects on ability to drive and use machines

< {INN name} has <no or negligible influence> <minor or moderate influence> <major influence> on the ability to drive and use machines.> [describe effects where applicable] <No studies on the effects on the ability to drive and use machines have been performed.> <Not relevant.>

4.8 Undesirable effects

Laboratory test findings (for example)
Post-marketing experience (for example)

4.9 Overdose

<No case of overdose has been reported.>

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification: {see SI 150 of 1991}
Mechanism of action
Microbiology (when applicable)
Drug resistance (when applicable)
Cross resistance (when applicable)

Pharmacodynamic effects

Adults
Paediatric patients

5.2 Pharmacokinetic properties

Absorption
Distribution
Biotransformation
Elimination
Characteristics in patients

5.3 Preclinical safety data

<Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.> <Preclinical effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.>

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

Mutagenicity
Carcinogenicity
Developmental Toxicity

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content (for example)
Capsule shell (for example) Printing ink (for example)

6.2 Incompatibilities

<Not applicable.>
<In the absence of compatibility studies, this pharmaceutical product must not be mixed with other pharmaceutical products.>
<This pharmaceutical product must not be mixed with other pharmaceutical products except those mentioned in 6.6.>

6.3 Shelf life

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

6.4 Special precautions for storage

<Do not store above <25°C> 30°C»
<Store at 2°C - 8°C (in a refrigerator» <Store in a freezer>
<Do not <refrigerate> <or> <freeze»
<Store in the original <package> <container» <Keep the container tightly closed>
<Keep the container in the outer carton>
<No special precautions for storage>
<in order to protect from <light> <moisture»

6.5 Nature and contents of container

<Not all pack sizes may be marketed.>

6.6 Instructions for use and handling <and disposal>

<No special requirements.>

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

7.1 NAME AND ADDRESS OF MANUFACTURER

7.2 NAME AND ADDRESS OF PRINCIPAL

8. REGISTRATION NUMBER
9. CATEGORY FOR DISTRIBUTION
10. DATE OF PUBLICATION OF THIS PACKAGE INSERT

ANNEX IV: QUANTITIES OF SAMPLES REQUIRED FOR LABORATORY ANALYSIS AND PRODUCT INFORMATION EVALUATION

The following is the minimum sample size required for analysis and information evaluation. However as a guiding principle the applicant should provide adequate sample for a full spectrum of analysis based on the proposed finished product specifications and repeat if required**.**

Nature of Product	Pack Size	Number of Containers
Tablets and Capsules	24 30 60 90 100 120 500 1000	6 5 4 4 4 3 3 3
Oral Suspensions	60 ml 100 ml 240 ml	5 5 4
Powders for Oral Suspensions	Market pack size	5
Sterile Solutions or Infusions e.g Sodium Chloride 0.9%w/v Intravenous Infusion	500 ml or less 1000 ml	10 5
Sterile Powders for Injections e.g. Penicillin G Sodium powder for injection	Powder in 2 ml vials Powder in 5 ml vials Powder in 10 ml vials	50 50 30
Injections	1 ml 2 ml 3 ml 5 ml 10 ml	100 50 50 20 20
Creams and Ointments	15 g 25 g 30 g ≥ 100 g	20 10 6 5

NB: Samples **MUST be** submitted in their original containers intended for marketing.

APPLICANTS please note:

1. Ensure that you have attached **Copy of the certificate of analysis CoA.**
2. Ensure that you have attached **Finished Product Specifications** & **Method of Analysis**
3. Ensure that you have provided all **Chemical Reference Standards**, **Decomposition products** and **Related substances** required for a full monograph analysis when submitting **Registration samples**.

ANNEX V: PRODUCT QUALITY REVIEW REQUIREMENTS FOR ESTABLISHED GENERIC PRODUCTS

For an established generic product, a product quality review may satisfy the requirements of Sections 3.2.P.2.2.1 (Formulation Development), 3.2.P.2.3 (Manufacturing Process Development) and 3.2.P.3.5 (Process Validation and/or Evaluation) of the PD and QOS-PD.

A product quality review should be submitted with the objective of verifying the consistency of the quality of the FPP and its manufacturing process. Rejected batches should not be included in the analysis but must be reported separately together with the reports of failure investigations, as indicated below. Reviews should be conducted with not less than 10 consecutive batches manufactured over the period of the last 12 months, or, where 10 batches were not manufactured in the last 12 months, not less than 25 consecutive batches manufactured over the period of the last 36 months and should include at least:

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

Notes

Reviews must include data from all batches manufactured during the review period. Data should be presented in tabular or graphical form (i.e. charts or graphs), when applicable.
The above is specific to the dossier assessment process requirements and does not relieve the applicant of related GMP requirements.

ANNEX VI - 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.