NAMIBIA MEDICINES REGULATORY COUNCIL

MINISTRY OF HEALTH AND SOCIAL SERVICES

APPLICATION FOR REGISTRATION OF A MEDICINE

NAMIBIA GUIDELINE FOR SUBMISSION OF APPLICATIONS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE IN COMMON TECHNICAL DOCUMENT FORMAT

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INTRODUCTION

1.1 Background

These guidelines are intended to assist applicants to generate and compile data for applications to register medicines in Namibia. To ensure that the Namibian Medicines Regulatory Council (NMRC) standards are aligned with global standards, these are based on the International Conference on Harmonisation of Technical Requirements for Registration of Human Medicines (ICH) guidelines on CTD format, and the World Health Organization (WHO) Guidelines for Registration of multisource (generic) medicines (WHO Technical Report Series, No. 970, 2012 Annex 4).

Through the ICH process, considerable harmonization has been achieved on the organization of the registration documents with the issuance of the CTD guideline. This recommended format in the CTD guideline for 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 guideline provides recommendations on the quality information for active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs) that should be submitted to NMRC 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 NMRC 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. Applicants should refer to appropriate ICH guidelines for detailed guidance on submission of efficacy and safety data to support applications for registration of medicines.

1.2 Objectives

These guidelines are intended to:

- assist applicants in the preparation of product dossiers by providing clear general guidance on the format of these dossiers;
- fully adopt the modular format of the CTD as developed by ICH; and
- 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 NMRC.

1.3 Scope

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

To determine the applicability of this format for a particular type of product, applicants should consult with NMRC.

1.4 General principles

To facilitate the preparation of the product dossiers (PD), this guideline is organized 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 in bold text, verbatim, with minor modifications to accommodate adopted WHO terminology notably:

- "Drug substance" is replaced with "active pharmaceutical ingredient" or "API";
- "Drug product" is replaced with "finished pharmaceutical product" or "FPP";
- "application" is replaced with "product dossier" or "PD";
- "combination product" is replaced with "fixed-dose combination" or "FDC";

Following the bold text of the M4Q (CTD-Q) guideline, additional guidance is provided in plain text to easily distinguish from the ICH text and is included to provide further clarity on NMRC's expectations for the content of PDs. This approach is intended to facilitate the identification and origin of the text in the guideline (i.e. from ICH or NMRC).

The content of this guideline should be read in conjunction with relevant information described in other existing NMRC (i.e. General guideline on preparation of dossiers in CTD format, Namibia CTD document), 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.

1.5 Guidance on format

The recommendations outlined in the Namibia Guideline for the preparation and submission of dossiers in common technical document format should be followed for the format and presentation of the PD. 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).

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

- the Open part (non-proprietary information) of each APIMF should always be included in its entirety in the PD, as an annex to 3.2.S.
- For a FPP containing more than one drug substance, the information requested for part "3.2.S" should be provided in its entirety for each API

- 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.
- 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 PD should be provided for each FPP strength.
- 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.
- for multiple FPPs (e.g. tablets and a parenteral product): a separate dossier is required for each FPP.
- 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.
- for a co-blistered FPP, one complete “3.2.P” section should be provided for each product.

ORGANIZATION OF A PRODUCT DOSSIER IN COMMON TECHNICAL DOCUMENT FORMAT

The CTD is organized into five modules. Module 1 is region/country-specific. Modules 2, 3, 4 and 5 are intended to be common. Conformance with these guidelines should ensure that Modules 2, 3, 4 and 5 are provided in a format acceptable to Namibia.
This section provides an overview of module contents for a multisource product in greater detail.

- Module 1: Administrative information and prescribing information — This module should contain documents specific to Namibia; for example, application forms or the proposed label for use in the region/country.
- Module 2: CTD summaries — This Module should begin with a general introduction to the pharmaceutical, 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 NMRC’s Quality overall summary — product dossier (QOS–PD) template
    - — The organization of these summaries is described in Guidelines for ICH M4, M4Q and M4S.
- Module 3: Quality — Information on quality should be presented in the structured format described in ICH M4Q
- Module 4: Nonclinical study reports
- Module 5: Clinical study reports — The human study reports and related information should be presented in the order described in ICH M4E and the SADC Regional Guidelines on Bioavailability and Bioequivalence.

MODULE 1 — ADMINISTRATIVE INFORMATION AND PRESCRIBING INFORMATION

The requirements for Module 1 are provided in the NMRC guidelines for preparation of product dossiers in CTD format.

MODULE 2: COMMON TECHNICAL DOCUMENT SUMMARIES

2.3: QUALITY OVERALL SUMMARY (QOS)

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

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

The Namibian Quality overall summary – product dossiers (QOS-PD) template should be completed for multisource (generic) and new chemical entities (NCEs) pharmaceutical (see 1.3 Scope for further clarification) and their corresponding FPPs. All sections and fields in the QOS-PD template that would be applicable should be completed. It is understood that certain sections and fields may not apply and should be indicated as such by reporting “not applicable” in the appropriate area with an accompanying explanatory note.

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

INTRODUCTION

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

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

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

Information from 3.2.S.1 should be included.

2.3.S.2 Manufacture (name, manufacturer)
Information from 3.2.S.2 should be included:

- Information on the manufacturer;
- A brief description of the manufacturing process (including, for example, reference to starting materials, critical steps, and reprocessing) and the controls that are intended to result in the routine and consistent production of material(s) of appropriate quality;
- A flow diagram, as provided in 3.2.S.2.2;
- A description of the Source and Starting Material and raw materials of biological origin used in the manufacture of the API, as described in 3.2.S.2.3;
- A discussion of the selection and justification of critical manufacturing steps, process controls, and acceptance criteria. Highlight critical process intermediates, as described in 3.2.S.2.4;
- A description of process validation and/or evaluation, as described in 3.2.S.2.5.
- A brief summary of major manufacturing changes made throughout development and conclusions from the assessment used to evaluate product consistency, as described in 3.2.S.2.6. The QOS should also cross-refer to the non-clinical and clinical studies that used batches affected by these manufacturing changes, as provided in the CTD-S and CTD-E modules of the dossier.

2.3.S.3 Characterization (name, manufacturer)

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

For Biotech: A description of the desired product and product-related substances and a summary of general properties, characteristic features and characterisation data (for example, primary and higher order structure and biological activity), as described in 3.2.S.3.1, should be included.

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

2.3.S.4 Control of API (name, manufacturer)
A brief summary of the justification of the specification(s), the analytical procedures, and validation should be included. Specification from 3.2.S.4.1 should be provided. A tabulated summary of the batch analyses from 3.2.S.4.4, with graphical representation where appropriate, should be provided.

2.3.S.5 Reference Standards or Materials (name, manufacturer)
Information from 3.2.S.5 (tabulated presentation, where appropriate) should be included.

2.3.S.6 Container Closure System (name, manufacturer)
A brief description and discussion of the information, from 3.2.S.6 should be included.

2.3.S.7 Stability (name, manufacturer)
This section should include a summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions, the proposed storage conditions, retest date or shelf-life, where relevant, as described in 3.2.S.7.1.
The post-approval stability protocol, as described in 3.2.S.7.2, should be included.
A tabulated summary of the stability results from 3.2.S.7.3, with graphical representation where appropriate, should be provided.

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

2.3.P.1 Description and Composition of the FPP (name, dosage form)
Information from 3.2.P.1 should be provided. Composition from 3.2.P.1 should be provided.

2.3.P.2 Pharmaceutical Development (name, dosage form)
A discussion of the information and data from 3.2.P.2 should be presented.
A tabulated summary of the composition of the formulations used in clinical trials and a presentation of dissolution profiles should be provided, where relevant.

2.3.P.3 Manufacture (name, dosage form)
Information from 3.2.P.3 should include:

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

2.3.P.4 Control of Excipients (name, dosage form)
A brief summary on the quality of excipients, as described in 3.2.P.4, should be included.

2.3.P.5 Control of FPP (name, dosage form)
A brief summary of the justification of the specification(s), a summary of the analytical procedures and validation, and characterisation of impurities should be provided. Specification(s) from 3.2.P.5.1 should be provided. A tabulated summary of the batch analyses provided under 3.2.P.5.4, with graphical representation where appropriate should be included.

2.3.P.6 Reference Standards or Materials (name, dosage form)
Information from 3.2.P.6 (tabulated presentation, where appropriate) should be included.

2.3.P.7 Container Closure System (name, dosage form)
A brief description and discussion of the information in 3.2.P.7 should be included.

2.3.P.8 Stability (name, dosage form)
A summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions of the stability studies and analysis of data should be included. Conclusions with respect to storage conditions and shelf-life and, if applicable, in- use storage conditions and shelf-life should be given.
A tabulated summary of the stability results from 3.2.P.8.3, with graphical representation where appropriate, should be included. The post-approval stability protocol, as described in 3.2.P.8.2, should be provided.

2.3.A APPENDICES

2.3.A.1 Facilities and Equipment (name, manufacturer)
Biotech: A summary of facility information described under 3.2.A.1 should be included.

2.3.A.2 Adventitious Agents Safety Evaluation (name, dosage form and manufacturer)
A discussion on measures implemented to control endogenous and adventitious agents in production should be included.
A tabulated summary of the reduction factors for viral clearance from 3.2.A.2, should be provided.

2.3.A.3 Excipients

2.3.R REGIONAL INFORMATION

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

2.4 NONCLINICAL OVERVIEW

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

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

2.5 CLINICAL OVERVIEW

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

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

2.6 NONCLINICAL WRITTEN AND TABULATED SUMMARIES

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

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

2.7 CLINICAL SUMMARY

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

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

MODULE 3: QUALITY

3.1. TABLE OF CONTENTS OF MODULE 3

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

3.2. BODY OF DATA

3.2.S ACTIVE PHARMACEUTICAL INGREDIENT (NAME, MANUFACTURER)

The API information can be submitted to Namibia in one of the following two options:

- Option 1: Certificate of suitability of the European Pharmacopoeia (CEP); or
- Option 2: Full details in the PD.

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

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

A complete copy of the CEP (including any annexes) should be provided in Module 3.2.R.3. The CEP holder on behalf of the FPP manufacturer or applicant should duly fill out the declaration of access for the CEP to the NMRC who refers to the CEP.

In addition, a written commitment should be included that the applicant will inform NMRC in the event that the CEP is withdrawn. It should also be acknowledged by the applicant that withdrawal of the CEP would require additional consideration of the API data requirements to support the PD. The written commitment should accompany the copy of the CEP in Module 3.2.R.3.

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

- 3.2.S.1.3 General properties - discussions on any additional applicable physicochemical and other relevant API properties that are not controlled by the CEP and Ph.Eur. monograph, e.g. solubilities and polymorphs as per guidance in this section.
- 3.2.S.3.1 Elucidation of structure and other characteristics - studies to identify polymorphs (exception: where the CEP specifies a polymorphic form) and particle size distribution, where applicable, as per guidance in this section.
- 3.2.S.4.1 Specification - the specifications of the FPP manufacturer including all tests and limits of the CEP and Ph.Eur. monograph and any additional tests and acceptance criteria that are not controlled in the CEP and Ph.Eur. monograph, such as polymorphs and/or particle size distribution.
- 3.2.S.4.2 / 3.2.S.4.3 Analytical procedures and validation – for any methods used by the FPP manufacturer in addition to those in the CEP and Ph.Eur. monograph.
- 3.2.S.4.4 Batch analysis - results from two batches of at least pilot scale, demonstrating compliance with the FPP manufacturer's API specifications.
- 3.2.S.5 Reference standards or materials – information on the FPP manufacturer's reference standards.
- 3.2.S.6 Container closure system - specifications including descriptions and identification of primary packaging components. Exception: where the CEP specifies a container closure system and the applicant declares to use the same container closure system.
- 3.2.S.7 Stability - exception: where the CEP specifies a re-test period that is the same as or of longer duration, and storage conditions which are the same or higher temperature and humidity as proposed by the applicant.

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

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 PD as outlined in the subsequent

sections of this guideline. The QOS-PD should be completed as per Section 3.1 of this guideline.

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

3.2.S.1.1 Nomenclature (name, manufacturer)

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

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

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

3.2.S.1.2 Structure (name, manufacturer)

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

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

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

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

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

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

The physical and chemical properties of the API should be discussed including the physical description, solubilities in common solvents (e.g. water, alcohols, dichloromethane, acetone), quantitative aqueous pH solubility profile (e.g. pH 1.2 to 6.8, dose/solubility volume), polymorphism, pH and pKa values, UV absorption maxima and molar absorptivity, melting point, refractive index (for a liquid), hygroscopicity, partition

coefficient, etc. (see table in the QOS-PD). This list is not intended to be exhaustive, but provides an indication as to the type of information that could be included.

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

Physical description

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

Solubilities/quantitative aqueous pH solubility profile

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

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

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

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

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

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

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

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

Polymorphism

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

- the polymorphic form(s) present in the proposed API should be listed in Section 3.2.S.1.3;
- the description of manufacturing process and process controls (3.2.S.2.2) should indicate which polymorphic form is manufactured, where relevant;
- the literature references or studies performed to identify the potential polymorphic

forms of the API, including the study results, should be provided in Section 3.2.S.3.1

- if a polymorphic form is to be defined or limited (e.g. for APIs that are not BCS highly soluble and/or where polymorphism has been identified as an issue), details should be included in 3.2.S.4.1 through 3.2.S.4.5.

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

Particle size distribution

As recommended in ICH's CTD-Q Questions and Answers/Location Issues document, the studies performed to identify the particle size distribution of the API should be provided in Section 3.2.S.3.1 (refer to this section of this guideline for additional information).

Information from literature

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

Reference ICH Guidelines: Q6A and Q6B

3.2.S.2 Manufacture (name, manufacturer)

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

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

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

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

A valid manufacturing authorization should be provided for the production of APIs. If available, a certificate of GMP compliance 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 drug substance manufacturing process represents the applicant's commitment for the manufacture of the drug substance. Information should be provided to adequately describe the manufacturing process and process controls. For example:

NCE: A flow diagram of the synthetic process (es) should be provided that

includes molecular formulae, weights, yield ranges, chemical structures of starting materials, intermediates, reagents and drug substance reflecting stereochemistry, and identifies operating conditions and solvents.

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

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

The following requirements apply to the second option 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 its choice justified by the manufacturer and accepted as such by assessors. The API starting material should be proposed taking into account the complexity of the molecule, the proximity of the API starting material to the final API, the availability of the API starting material as a commercial chemical and the quality controls placed upon the API starting material. This justification should be documented in the dossier and be available for review by NMRC GMP inspectors.

In situations where the API starting material is a complex molecule and only a minimal number of synthetic steps from the final API, a further molecule called the starting material for synthesis should be proposed and its choice justified by the applicant. The starting material for synthesis defines the starting point in the manufacturing process for an API to be described in an application. The applicant should propose and justify which substances should be considered as starting materials for synthesis. See section 3.2.S.2.3 for further guidance. In the case where the precursor to the API is obtained from fermentation, or is from plant or animal origin, such a molecule can be considered the API starting material regardless of complexity.

A one step synthesis may be accepted in exceptional cases, for example where the API starting material is covered by a CEP, or when the structure of the API is so simple that a one step synthesis can be justified, e.g. ethambutol or ethionamide.

In addition to the detailed description of the manufacturing process as per ICH M4Q, the recovery of materials, if any, should be described in detail with the step in which they are introduced into the process. Recovery operations should be adequately controlled such that impurity levels do not increase over time. For recovery of solvents, any processing

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

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

All solvents used in the manufacture (including purification and/or crystallization step(s)) should be clearly identified. Solvents used in the final steps should be of high purity. Use of recovered solvents in the final steps of purification and/or crystallization is not recommended, however their use can be justified on presentation of sufficient data demonstrating that recovered solvents meet appropriate standards as outlined in ICH Q7.

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

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

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

It is acceptable to provide information on pilot scale manufacture, provided it is representative of production scale and scale-up is reported immediately to WHO according to the requirements of the NMRC variation guideline and WHO variation guideline (ref: WHO Technical Report Series, No. 943, Annex 6).

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

<u>Batch(es) and scale definition</u>
An explanation of the batch numbering system, including information regarding any pooling of harvests or intermediates and batch size or scale should be provided.

<u>Cell culture and harvest</u>
A flow diagram should be provided that illustrates the manufacturing route from

the original inoculum (e.g. cells contained in one or more vials(s) of the Working Cell Bank up to the last harvesting operation. The diagram should include all steps (i.e., unit operations) and intermediates. Relevant information for each stage, such as population doubling levels, cell concentration, volumes, pH, cultivation times, holding times, and temperature, should be included. Critical steps and critical intermediates for which specifications are established (as mentioned in 3.2.S.2.4) should be identified.

A description of each process step in the flow diagram should be provided. Information should be included on, for example, scale; culture media and other additives (details provided in 3.2.S.2.3); major equipment (details provided in 3.2.A.1); and process controls, including in-process tests and operational parameters, process steps, equipment and intermediates with acceptance criteria (details provided in 3.2.S.2.4). Information on procedures used to transfer material between steps, equipment, areas, and buildings, as appropriate, and shipping and storage conditions should be provided. (Details on shipping and storage provided in 3.2.S.2.4.)

<u>Purification and modification reactions</u>
A flow diagram should be provided that illustrates the purification steps (i.e., unit operations) from the crude harvest(s) up to the step preceding filling of the drug substance. All steps and intermediates and relevant information for each stage (e.g., volumes, pH, critical processing time, holding times, temperatures and elution profiles and selection of fraction, storage of intermediate, if applicable) should be included. Critical steps for which specifications are established as mentioned in 3.2.S.2.4 should be identified.

A description of each process step (as identified in the flow diagram) should be provided. The description should include information on, for example, scale, buffers and other reagents (details provided in 3.2.S.2.3, major equipment (details provided in 3.2.A.1), and materials. For materials such as membranes and chromatography resins, information for conditions of use and reuse also should be provided. (Equipment details in 3.2.A.1; validation studies for the reuse and regeneration of columns and membranes in 3.2.S.2.5.) The description should include process controls (including in-process tests and operational parameters) with acceptance criteria for process steps, equipment and intermediates. (Details in 3.2.S.2.4.)

Reprocessing procedures with criteria for reprocessing of any intermediate or the drug substance should be described. (Details should be given in 3.2.S.2.5.)
Information on procedures used to transfer material between steps, equipment, areas, and buildings, as appropriate, and shipping and storage conditions should be provided (details on shipping and storage provided in 3.2.S.2.4.).

Filling, storage and transportation (shipping) A description of the filling procedure for the drug substance, process controls (including in- process tests and

operational parameters), and acceptance criteria should be provided. (Details in 3.2.S.2.4.) The container closure system(s) used for storage of the drug substance (details in 3.2.S.6.) and storage and shipping conditions for the drug substance should be described.

Reference ICH Guidelines: Q5A, Q5B, and Q6B

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

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

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

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

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

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

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

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

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

When available, a CEP demonstrating TSE-compliance should be provided. A complete copy of the CEP (including any annexes) should be provided in Module 3.2.R.3.

Reference ICH Guidelines: Q6A and Q6B

Biotech:
Control of Source and Starting Materials of Biological Origin
Summaries of viral safety information for biologically sourced materials should be provided. (Details in 3.2.A.2.)

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

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

Reference ICH Guidelines: Q5A, Q5B, Q5C and Q5D

3.2.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 ICH Guidelines: Q6A and Q6B

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

Reference ICH Guideline: Q5C

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

Process validation and/or evaluation studies for aseptic processing and sterilisation 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 sterilization methods. The controls used to maintain the sterility of the API during storage and transportation should also be provided. Alternate processes should be justified and described (see guidance in 3.2.S.2.2 for the level of detail expected).

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

The plan for conducting the study should be described and the results, analysis and conclusions from the executed study(ies) should be provided. The analytical procedures and corresponding validation should be cross-referenced (e.g., 3.2.S.2.4, 3.2.S.4.3) or provided as part of justifying the selection of critical process controls and acceptance criteria.

For manufacturing steps intended to remove or inactivate viral contaminants, the information from evaluation studies should be provided in 3.2.A.2.

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

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

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

Reference ICH Guideline: Q3A

Biotech:

The developmental history of the manufacturing process, as described in 3.2.S.2.2, should be provided. The description of change(s) made to the manufacture of drug substance batches used in support of the marketing application (e.g., nonclinical or clinical studies) should include, for example, changes to the process or to critical equipment. The reason for the change should be explained. Relevant information on drug substance batches manufactured during development, such as the batch number, manufacturing scale, and use (e.g., stability, nonclinical, reference material) in relation to the change, should be provided.

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

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

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

Reference ICH Guideline: Q6B

3.2.S.3 Characterisation (name, manufacturer)

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

NCE & Generics:

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

Elucidation of structure

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

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

For APIs that are described in an officially recognized pharmacopoeia, it is generally sufficient to provide copies of the IR spectrum of the API from each of the proposed manufacturer(s) run concomitantly with an officially recognized pharmacopoeial 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 clinical or comparative biostudies, and information should be given as to the stereoisomer of the API that is to be used in the FPP.

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

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

When a single enantiomer of the API is claimed for non-pharmacopoeial APIs,

unequivocal proof of absolute configuration of asymmetric centers should be provided such as determined by X-ray of a single crystal.

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

Polymorphism

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

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

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

Applicants to the NMRC and API manufacturers are expected to have adequate knowledge about the polymorphism of the APIs used and/or produced. Information on polymorphism can come from the scientific literature, patents, compendia or other references to determine if polymorphism is a concern, e.g. for APIs that are not BCS highly soluble. In the absence of published data for APIs that are not BSC highly soluble, polymorphic screening will be necessary to determine if the API can exist in more than one crystalline form. Polymorphic screening is generally accomplished via crystallization studies using different solvents and conditions.

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

Decision tree 4(1) of ICH Q6A can be used where screening is necessary and 4(2) can be used to investigate if different polymorphic forms have different properties that may affect performance, bioavailability and stability of the FPP and to decide whether a

preferred polymorph should be monitored at release and on storage of the API. Where there is a preferred polymorph, acceptance criteria should be incorporated into the API specification to ensure polymorphic equivalence of the commercial material and that of the API batches used in the comparative bioavailability or biowaiver studies. The polymorphic characterization of the API batches used in clinical or comparative bioavailability or biowaiver studies by the above-mentioned methods should be provided. The method used to control polymorphic form should be demonstrated to be specific for the preferred form.

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

- specifications for the solvent-free API in 3.2.S.2.4, if that compound is a synthetic precursor;
- specifications for the solvated API including appropriate limits on the weight ratio of API to solvent (with data to support the proposed limits);
- a description of the method used to prepare the solvate in 3.2.S.2.2.

Particle size distribution

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

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

- d10 not more than (NMT) 10% of total volume less than X µm
- d50 XX µm - XXX µm
- d90 not less than (NLT) 90% of total volume less than XXXX µm.

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

Reference ICH Guideline: Q6A

Biotech:

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

Reference ICH Guideline: Q6B

3.2.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 pharmacopoeial standard is claimed, a discussion should be provided of the potential and actual impurities arising from the synthesis, manufacture, or degradation of the API. This should cover starting materials, by-products, intermediates, chiral impurities and degradation products and should include the chemical names, structures and origins. The discussion of pharmacopoeial APIs should not be limited to the impurities specified in the API monograph.

The tables in the QOS-PD template should be used to summarize the information on the API- related 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 recognized by the pharmacopoeias that APIs can be obtained from various sources and thus can contain impurities not considered during the development of the monograph. Furthermore, a change in the production or source may give rise to additional impurities that are not adequately controlled by the official compendial monograph. As a result, each 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 recognized pharmacopoeia is generally considered to be qualified. The following is an additional option for qualification of impurities in existing APIs:

> The limit for an impurity present in an existing API can be accepted by comparing the impurity results found in the existing API with those observed in an innovator product using the same validated, stability-indicating analytical procedure (e.g. comparative HPLC studies). If samples of the innovator product are not available, the impurity profile may also be compared to a different prequalified FPP with the same route of administration and similar characteristics (e.g. tablet versus capsule). It is recommended that the studies be conducted on comparable samples (e.g. age of samples) to obtain a meaningful comparison of the impurity profiles.
>
> Levels of impurities generated from studies under accelerated or stressed storage conditions of the innovator or prequalified FPP are not considered acceptable/qualified.
>
> A specified impurity present in the existing API is considered qualified if the amount of the impurity in the existing API reflects the levels observed in the innovator or prequalified FPP.

Basis for setting the acceptance criteria

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

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

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

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

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

The absence of known established highly toxic impurities (genotoxic) used in the process or formed as a by-product should be discussed and suitable limits should be proposed. The limits should be justified by appropriate reference to available guidances (e.g. EMEA/CHMP/QWP/251344/2006 or USFDA Guidance for Industry: Genotoxic and carcinogenic impurities in drug substances and products, recommended approaches, December 2008) 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 recognized pharmacopoeias that cover metal contamination originating from manufacturing equipment and the environment.

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

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

3.2.S.4.1 Specification (name, manufacturer)

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

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

- The standard declared by the applicant could be an officially recognized compendial standard (e.g. Ph.Int., Ph.Eur., BP, USP, JP) 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, JP, in-house) and the version (e.g. code number/version/date) should be provided for version control purposes.

In cases where there is more than one API manufacturer, the FPP manufacturer's API specifications should be one single compiled set of specifications that is identical for

each manufacturer. It is acceptable to lay down in the specification more than one acceptance criterion and/or analytical method for a single parameter with the statement "for API from manufacturer A" (e.g. in the case of residual solvents).

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

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

Reference ICH Guidelines: Q6A and Q6B, officially recognized pharmacopeia

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

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

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

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

Although HPLC is normally considered the method of choice for determining API-related impurities, other chromatographic methods such as GC and TLC can also be used, if appropriately validated. For determination of related substances, reference standards should normally be available for each of the identified impurities; particularly those known to be toxic and the concentration of the impurities should be quantitated against their own reference standards. Impurity standards may be obtained from pharmacopoeias (individual impurities or resolution mixtures), from commercial sources or prepared in-house. It is considered acceptable to use the API as an external standard to estimate the levels of impurities, provided the response factors of those impurities are sufficiently close to that of the API, i.e. between 80 and 120%. In cases where the response factor is outside this range, it may still be acceptable to use the API, provided a correction factor is applied. Data to support calculation of the correction factor should be provided for an in-house method. Unspecified impurities may be quantitated using a solution of the API as the reference standard at a concentration corresponding to the limit established for individual unspecified impurities (e.g. 0.10%). The test for related substances in the Ph.Int. monograph for lamivudine serves as a typical example.

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

Reference ICH Guidelines: Q2A and Q6B, WHO Technical Report Series, No. 943, Annex 3

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

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

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

Tables for summarizing a number of the different analytical procedures and validation information (e.g. HPLC assay/impurity methods, GC methods) can be found in the 2.3.R Regional information section of the QOS-PD (i.e. 2.3.R.2). These tables should be used to summarize the validation information of the analytical procedures of the FPP manufacturer for determination of residual solvents, assay and purity of the API, in section 2.3.S.4.3 of the QOS-PD. The validation data for other methods used to generate assay and purity data in the PD can be summarized in 2.3.S.4.4 (c) or 2.3.S.7.3 (b) of the QOS-PD.

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

In general verification is not necessary for compendial API assay methods. However, specificity of a specific compendial assay method should be demonstrated if there are any potential impurities that are not specified in the compendial monograph. If an

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

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

Reference ICH Guidelines: Q2A, Q2B, and Q6B

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, preclinical and clinical data (if relevant), stability, pilot, scale-up and, if available, production-scale batches. This data is used to establish the specifications and evaluate consistency in API quality.

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

Copies of the certificates of analysis, both from the API manufacturer(s) and the FPP manufacturer, should be provided for the profiled batches and any company responsible for generating the test results should be identified. The FPP manufacturer's test results should be summarized in the QOS-PD.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as "all tests meet specifications". For quantitative tests (e.g. individual and total impurity tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements such as "within limits" or "conforms".

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

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

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

Justification for the drug substance specification should be provided.

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

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

Reference ICH Guidelines: Q3A, Q3C, Q6A and Q6B, officially recognized pharmacopeia

3.2.S.5 Reference Standards or Materials (name, manufacturer)
Information on the reference standards or reference materials used for testing of the drug substance should be provided.

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

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

A suitable primary reference standard should be obtained from an officially recognized pharmacopoeial source (e.g. Ph.Int., Ph.Eur., BP, USP, JP) where one exists and the lot number should be provided. Where a pharmacopoeial standard is claimed for the API and/or the FPP, the primary reference standard should be obtained from that pharmacopoeia when available. Primary reference standards from officially recognized pharmacopoeial sources do not need further structural elucidation.

Otherwise, a primary standard may be a batch of the API that has been fully characterized (e.g. by IR, UV, NMR, MS analyses). Further purification techniques may be needed to render the material acceptable for use as a chemical reference standard. The purity requirements for a chemical reference substance depend upon its intended use. A chemical reference substance proposed for an identification test does not require meticulous purification, since the presence of a small percentage of impurities in the substance often has no noticeable effect on the test. On the other hand, chemical reference substances that are to be used in assays should possess a high degree of purity (such as 99.5% on the dried or water/solvent free basis). Absolute content of the primary reference standard must be declared and should follow the scheme: 100% minus organic impurities (quantitated by an assay procedure, e.g. HPLC, DSC, etc.) minus inorganic impurities minus volatile impurities by loss on drying (or water content minus residual solvents).

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

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

Reference ICH Guidelines: Q6A and Q6B, 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 drug substance, including sorption to container and leaching, and/or safety of materials of construction.

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

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 relabeling 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 summarized. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate.

The WHO guideline Stability testing of active pharmaceutical ingredients and finished pharmaceutical products (WHO Technical Report Series, No. 953, Annex 2) should be consulted for recommendations on the core stability data package required for the prequalification of APIs and FPPs.

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

Stress testing

As outlined in the ICH Q1A guidance document, stress testing of the API can help identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual API and the type of FPP involved.

Stress testing may be carried out on a single batch of the API. For examples of typical stress conditions refer to WHO Technical Report Series, No. 953, Annex 2, Section 2.1.2, as well as, "A typical set of studies of the degradation paths of an active pharmaceutical ingredient" 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 non- degraded API. This target is chosen so that some degradation occurs, but not enough to generate secondary products. For this reason, the conditions and duration may need to be varied when the API is especially susceptible to a particular stress factor. In the total absence of degradation products after 10 days, the API is considered stable under the particular stress condition.

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

highlight whether mass balance was observed.

Photostability testing should be an integral part of stress testing. The standard conditions are described in ICH Q1B. If “protect from light” is stated in one of the officially recognized pharmacopoeia for the API, it is sufficient to state “protect from light” on labelling, in lieu of photostability studies, when the container closure system is shown to be light protective.

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

Accelerated and long-term testing

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

The required long-term storage conditions for APIs in the Prequalification Programme is either 30°C±2°C/65%±5%RH or 30°C±2°C/75%±5%RH. Studies covering the proposed re- test period at the above mentioned long-term storage conditions will provide better assurance of the stability of APIs at the conditions of the supply chain corresponding to the WHO and Prequalification Programme environments. Alternative conditions should be supported with appropriate evidence, which may include literature references or in-house studies, demonstrating that storage at 30°C is inappropriate for the API. For APIs intended for storage in a refrigerator and those intended for storage in a freezer refer to the 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 re-test period, data should be provided on not less than three batches of at least pilot scale. The same synthesis route as production batches and using a method of manufacture and procedure simulating the final process to be used for production batches should be used for the stability 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)

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

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

Refer to 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 re-test period

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

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

After this re-test period, a batch of API destined for use in the manufacture of an FPP could be re-tested and then, if in compliance with the specification, could be used immediately (e.g. within 30 days). If re-tested and found compliant, the batch does not receive an additional period corresponding to the time established for the re-test period. However, an API batch can be re-tested multiple times and a different portion of the batch used after each re-test, as long as it continues to comply with the specification. For APIs known to be labile (e.g. certain antibiotics), it is more appropriate to establish a shelf life rather than a re-test period (reference: ICH Q1A).

Limited extrapolation of the real time data from the long-term storage condition beyond the observed range to extend the re-test period can be undertaken at the time of assessment of the 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 re-test period could be up to two times the period covered by the long-term data, but should not exceed the long-term data by 12 months).

Reference ICH Guidelines: Q1A, Q1B, and Q5C, 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 re-test period granted at the time of assessment of the PD, a commitment should be made to continue the stability studies in order to firmly establish the re-test period. A written commitment (signed and dated) to continue long-term testing over the re-test period should be included in the dossier when relevant.

Commitment stability studies

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

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

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

Ongoing stability studies

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

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

Refer to 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 ICH Guidelines: Q1A and Q5C, 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 re-test period should be included in the dossier. For quantitative tests (e.g. individual and total degradation product tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements such as “within limits” or “conforms”.

Reference ICH Guidelines: Q1A, Q1B, Q1D, Q1E, Q2A, Q2B, and Q5C, WHO Technical Report Series, No. 953, Annex 2

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

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

A description of the drug product 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-PD template should be used to summarize the composition of the FPP and express the quantity of each component on a per unit basis (e.g. mg per tablet, mg per ml, mg per vial) and percentage basis, including a statement of the total weight or measure of the dosage unit. The individual components for mixtures prepared in-house (e.g. coatings) should be included in the tables, where applicable.

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

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

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

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

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

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

- ***Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable.***
  The container closure used for the FPP (and accompanying reconstitution diluent, if applicable) should be briefly described, with further details provided under 3.2.P.7 Container closure system, e.g.
  > “The product is available in HDPE bottles with polypropylene caps (in sizes of 100‟s, 500‟s and 1000‟s) and in PVC/Aluminum foil unit dose blisters (in packages of 100‟s (cards of 5x2, 10 cards per package).”

Reference ICH Guidelines: Q6A and Q6B

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

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

Pharmaceutical development information should include, at a minimum:

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

  These features should be discussed as part of the product development using the principles of risk management over the entire lifecycle of the product (ref: ICH Q8).

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

Reference ICH Guidelines: Q6A and Q6B, Q8, Q9, Q10, WHO Technical Report Series, No. 929, Annex 5,

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

3.2.P.2.1.1 API (name, dosage form)

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

substance that can influence the performance of the drug product should be discussed. For combination products, the compatibility of drug substances with each other should be discussed.

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

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

3.2.P.2.1.2 Excipients (name, dosage form)
The choice of excipients listed in 3.2.P.1, their concentration, their characteristics that can influence the drug product performance should be discussed relative to their respective functions.

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

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

Where antioxidants are included in the formulation, the effectiveness of the proposed concentration of the antioxidant should be justified and verified by appropriate studies.
Antimicrobial preservatives are discussed in 3.2.P.2.5.

3.2.P.2.2 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 clinical formulations and the formulation (i.e. composition)

described in 3.2.P.1 should be discussed. Results from comparative in vitro studies (e.g., dissolution) or comparative in vivo studies (e.g., bioequivalence) should be discussed when appropriate.

NMRC 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 Appendix 2.

The requirements for bioequivalence studies should be taken into consideration for example when formulating multiple strengths and/or when the product(s) may be eligible for a biowaiver. WHO reference documents (e.g. SADC bioequivalence guideline, WHO Technical Report Series, No. 937, Annex 7) should be consulted.

Product scoring may be recommended or required, or is specified for an FPP in the listing of WHO recommended comparator products, or when division into fractional doses may be necessary according to approved posology.

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

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

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

In vitro dissolution or drug release

A discussion should be included as to how the development of the formulation relates to development of the dissolution method(s) and the generation of the dissolution profile. The results of studies justifying the choice of in vitro dissolution or drug release conditions (e.g. apparatus, rotation speed, medium) should be provided. Data should also be submitted to demonstrate whether the method is sensitive to changes in manufacturing processes and/or changes in grades and/or amounts of critical excipients and particle size where relevant. The dissolution method should be sensitive to any changes in the product that would result in a change in one or more of the pharmacokinetic parameters. Use of a single point test or a dissolution range should be justified based on the solubility and/or biopharmaceutical classification of the API.

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

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

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

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

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

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

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

Overages for the sole purpose of extending the shelf-life of the FPP are 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.

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 sterilization methods over terminal sterilization should be provided.

Differences between the manufacturing process(es) used to produce pivotal clinical batches and the process described in 3.2.P.3.3 that can influence the performance of the product should be discussed.

For products that meet the criteria of an established multisource product, in order to fulfil 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 Appendix 2. The guidance that follows applies to all other products, for which section P.2.3 should be completed in its entirety.

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

The scientific rationale for the selection, optimization and scale-up of the manufacturing process described in 3.2.P.3.3 should be explained, in particular the critical aspects (e.g. rate of addition of granulating fluid, massing time, granulation end-point). A discussion of the critical process parameters (CPP), controls and robustness with respect to the QTPP and CQA of the product should be included (ref: ICH Q8).

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

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

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

for example the following:

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

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

	Solid oral products	Oral liquid and topical products	Sterile products (including ophthalmics)
Description of any additional treatments*	X	X	X (sterilization and depyrogenation of the components)
Extraction studies	---	X	X
Interaction studies (Migration/Sorption)	---	X	X
Moisture permeability	X (uptake)	X (usually loss)	X (usually loss)
Light transmission	X**	X	X

*e.g. coating of tubes, siliconization of rubber stoppers, 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 multidose container is administered by means of a device suitable for measuring the prescribed volume. The device is usually a spoon or a cup for volumes of 5 ml or multiples thereof, or an oral syringe for other volumes or, for oral drops, a suitable dropper."

For a device accompanying a multidose container, the results of a study should be provided demonstrating the reproducibility of the device (e.g. consistent delivery of the

intended volume), generally at the lowest intended dose.

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

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

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

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

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

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

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

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

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

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

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

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

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

The list of manufacturers/companies should specify the actual addresses of production or manufacturing site(s) involved (including block(s) and unit(s)), rather than the administrative offices.

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

A valid manufacturing authorization for pharmaceutical production, as well as a marketing authorization, should be submitted to demonstrate that the product is registered or licensed in accordance with national requirements (Module 1, 1.2.2).

For each site where the major production step(s) are carried out, when applicable, attach a WHO-type 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, 1.7.6).

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

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

Regulatory situation in other countries
The countries should be listed in which this product has been granted a marketing authorization, this product has been withdrawn from the market and/or this application for marketing has been rejected, deferred or withdrawn (Module 1, 1.7.6).

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

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

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

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

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

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

3.2.P.3.3 Description of Manufacturing Process and Process Controls (name, dosage form)

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

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

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

The maximum holding time for 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 summarized in the QOS-PD template and should reflect the production of the proposed commercial batches. See Glossary for definitions of pilot-scale 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 sterilization parameters for equipment, container/closure, terminal sterilization etc.

Additionally for Biotech see 3.2.A.1 for facilities, if appropriate.

Reference ICH Guideline: Q6B, Q8, Q9, Q10

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

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

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

Examples of applicable in-process controls include:

- granulations: moisture (limits expressed as a range), blend uniformity (e.g. low dose tablets), bulk and tapped densities, particle size distribution;
- solid oral products: average weight, weight variation, hardness, thickness,

friability, and disintegration checked periodically throughout compression, weight gain during coating;
- semi-solids: viscosity, homogeneity, pH;
- transdermal dosage forms: assay of API-adhesive mixture, weight per area of coated patch without backing;
- metered dose inhalers: fill weight/volume, leak testing, valve delivery;
- dry powder inhalers: assay of API-excipient blend, moisture, weight variation of individually contained doses such as capsules or blisters;
- liquids: pH, specific gravity, clarity of solutions; and
- parenterals: appearance, clarity, fill volume/weight, pH, filter integrity tests, particulate matter, leak testing of ampoules, pre-filtration and/or pre-sterilization bioburden testing.

Reference ICH Guidelines: Q2A, Q2B, Q6A, and Q6B, 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 3.2.A.2, if necessary.

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

The following information should be provided for all other products:

a) a copy of the process validation protocol, specific to this FPP, described below;

b) a commitment that three consecutive, production-scale batches of this FPP will be subjected to prospective validation in accordance with the above protocol; The applicant should submit a written commitment that information from these studies will be available for verification after prequalification by the WHO inspection team; and

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

One of the most practical forms of process validation, mainly for non-sterile products, is the final testing of the product to an extent greater than that required in routine quality control. It may involve extensive sampling, far beyond that called for in routine quality control and testing to normal quality control specifications and often for certain parameters only. Thus, for instance, several hundred tablets per batch may be weighed

to determine unit dose uniformity. The results are then treated statistically to verify the "normality" of the distribution and to determine the standard deviation from the average weight. Confidence limits for individual results and for batch homogeneity are also estimated. Strong assurance is provided that samples taken at random will meet regulatory requirements if the confidence limits are well within compendial specifications.

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

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

- a reference to the current master production document;
- a discussion of the critical equipment;
- the process parameters that can affect the quality of the FPP (critical process parameters (CPPs)) including challenge experiments and failure mode operation;
- details of the sampling: sampling points, stages of sampling, methods of sampling and the sampling plans (including schematics of blender/storage bins for uniformity testing of the final blend);
- the testing parameters/acceptance criteria including in-process and release specifications and including comparative dissolution profiles of validation batches against the batch(es) used in the bioavailability or biowaiver studies;
- the analytical procedures or a reference to appropriate section(s) of the dossier;
- the methods for recording/evaluating results; and
- the proposed 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, sterilization and depyrogenation of containers, closures and equipment;
b) filtration of solutions;
c) lyophilization process;
d) leaker test of filled and sealed ampoules;
e) final inspection of the product; and
f) sterilization cycle.

The sterilization process used to destroy or remove microorganisms is probably the single most important process in the manufacture of parenteral FPPs. The process can make use of moist heat (e.g. steam), dry heat, filtration, gaseous sterilization (e.g. ethylene oxide), or radiation. It should be noted that terminal steam sterilization, when practical, is considered to be the method of choice to ensure sterility of the final FPP. Therefore, scientific justification for selecting any other method of sterilization should be provided.

The sterilization process should be described in detail and evidence should be provided to confirm that it will produce a sterile product with a high degree of reliability and that the physical and chemical properties as well as the safety of the FPP will not be affected. Details such as 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 processing of parenteral products that cannot be terminally sterilized, simulation process trials should be conducted. This involves filling containers with culture media under normal conditions, followed by incubation. Refer to current WHO GMP guidelines for details.

Reference ICH Guideline: Q6B, Q8, Q9, Q10, WHO Technical Report Series, No. 961, Annex 3

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

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

The specifications for excipients should be provided.

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

If the standard claimed for an excipient is an officially recognized compendial standard, it is sufficient to state that the excipient is tested according to the requirements of that standard, rather than reproducing the specifications found in the officially recognized compendial monograph.

If the standard claimed for an excipient is a non-compendial standard (e.g. House

standard) or includes tests that are supplementary to those appearing in the officially recognized compendial monograph, a copy of the specification for the excipient should be provided.

For generic products, only excipients with an officially recognized pharmacopoeial monograph should be used. Exceptions may 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”, the EU “List of permitted food colours”, and the FDA “Inactive ingredient guide”. For proprietary mixtures, the supplier‟s product sheet with the qualitative formulation should be submitted, in addition to the FPP manufacturer‟s specifications for the product including identification testing.

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

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

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 ICH Guideline: Q6A and Q6B

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

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

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

Reference ICH Guidelines: Q2A and Q6B

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

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

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

Reference ICH Guidelines: Q2A, Q2B, and Q6B

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

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

A discussion of the tests that are supplementary to those appearing in the officially recognized compendial monograph should be provided.

Reference ICH Guidelines: Q3C and Q6B

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

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

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

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

Materials of animal origin should be avoided whenever possible.

When available, a CEP demonstrating TSE-compliance should be provided. A complete copy of the CEP (including any annexes) should be provided in Module 3.2.R.3.

Reference ICH Guidelines: Q5A, Q5D, and 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 a drug product or by a new route of administration, full details of manufacture, characterisation, and controls, with cross references to supporting safety data (nonclinical and/or clinical) should be provided according to the drug substance format. (Details in 3.2.A.3).

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 drug product 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 authorized 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 summarized according to the tables in the QOS-PD template including the tests, acceptance criteria and analytical procedures (including types, sources and versions for the methods):

- the standard declared by the applicant could be an officially recognized compendial standard (e.g. Ph.Int., BP, USP, JP) or a House (manufacturer's) standard;
- the specification reference number and version (e.g. revision number and/or date) should be provided for version control purposes;
- for the analytical procedures, the type should indicate the kind of analytical procedure used (e.g. visual, IR, UV, HPLC), the source refers to the origin of the analytical procedure (e.g. Ph.Int., Ph.Eur., BP, USP, JP, in-house) and the version (e.g. code number/version/date) should be provided for version control purposes.

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

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

- fixed-dose combination FPPs (FDC-FPPs):
    - analytical methods that can distinguish each API in the presence of the other API(s) should be developed and validated,
    - acceptance criteria for degradation products should be established with reference to the API they are derived from. If an impurity results from a chemical reaction between two or more APIs, its acceptance limits should

in general be calculated with reference to the worst case (the API with the smaller area under the curve). Alternatively the content of such impurities could be calculated in relation to their reference standards,
    - a test and limit for content uniformity is required for each API present in the FPP at less than 5 mg or less than 5% of the weight of the dosage unit,
    - for the API(s) present at equal or greater than 5 mg and equal or greater than 5% of the weight of the dosage unit, a test and limit for weight variation may be established in lieu of content uniformity testing;
- modified-release products: a meaningful API release method;
- inhalation and nasal products: consistency of delivered dose (throughout the use of the product), particle or droplet size distribution profiles (comparable to the product used in in vivo studies, where applicable) and if applicable for the dosage form, moisture content, leak rate, microbial limits, preservative assay, sterility and weight loss;
- suppositories: uniformity of dosage units, melting point; and
- transdermal dosage forms: peal or shear force, mean weight per unit area, dissolution.

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

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

Skip testing is acceptable for parameters such as identification of colouring materials and microbial limits, when justified by the submission of acceptable supportive results for five production batches. When skip-testing justification has been accepted, the specifications should include a footnote, stating at minimum the following skip testing requirements: at minimum every tenth batch and at least one batch annually is tested. In addition, for stability- indicating parameters such as microbial limits, testing will be performed at release and shelf- life during stability studies.

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

Reference ICH Guidelines: Q3B, Q3C, Q6A and Q6B

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

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

Copies of the in-house analytical procedures used during pharmaceutical development (if used to generate testing results provided in the PD) as well as those proposed for

routine testing should be provided. Unless modified, it is not necessary to provide copies of officially recognized compendial analytical procedures.

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

Refer to section 3.2.S.4.2 of this guideline for additional guidance on analytical procedures.

Reference ICH Guidelines: Q2A and Q6B

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

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

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

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

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

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

If an officially recognized compendial standard is claimed and an in-house method is used in lieu of the compendial method (e.g. for assay or for related compounds), equivalency of the in-house and compendial methods should be demonstrated. Performing duplicate analyses of one sample by both methods and providing the results

from the study could accomplish this. For related compound methods, the sample analyzed should be the placebo spiked with related compounds at concentrations equivalent to their specification limits.

Reference ICH Guidelines: Q2A, Q2B and Q6B.

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

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

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

Analytical results tested by the company responsible for the batch release of the FPP (generally, the applicant or the FPP manufacturer, if different from the applicant) should be provided for not less than two batches of at least pilot scale, or in the case of an uncomplicated2 FPP (e.g. immediate-release solid FPPs (with noted exceptions), non-sterile solutions), not less than one batch of at least pilot scale and a second batch which may be smaller (e.g. for solid oral dosage forms, 25 000 or 50 000 tablets or capsules) of each proposed strength of the FPP. These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

The testing results should include the batch (es) used in the comparative bioavailability or biowaiver studies. Copies of the certificates of analysis for these batches should be provided in the 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 ICH Guidelines: Q3B, Q3C, Q6A, and Q6B

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

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

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

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

3.2.P.5.6 Justification of Specification(s) (name, dosage form)
Justification for the proposed drug product specification(s) should be provided.

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

The justification for certain tests, analytical procedures and acceptance criteria (e.g. degradation products, dissolution method development) may have been discussed in other sections of the 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.

Reference ICH Guidelines: Q3B, Q6A, and Q6B

3.2.P.6 Reference Standards or Materials (name, dosage form)
Information on the reference standards or reference materials used for testing of the drug product should be provided, if not previously provided in "3.2.S.5 Reference Standards or Materials".

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

Reference ICH Guidelines: Q6A and Q6B, WHO Technical Report Series, No. 943, Annex 3

3.2.P.7Container Closure System (name, dosage form)
A description of the container closure systems should be provided, including the identity of materials of construction of each primary packaging component and its specification. The specifications should include description and identification (and critical dimensions, with drawings where appropriate). Non-compendial

methods (with validation) should be included where appropriate.

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

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

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

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

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

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

The specifications for the primary packaging components should include a specific test for identification (e.g. IR). Specifications for film and foil materials should include limits for thickness or area weight.

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

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

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

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

The SADC Stability guideline, 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 prequalification of APIs and FPPs.

As outlined in the SADC Stability guideline, 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 programme also includes the study of product-related factors that influence its quality, for example, interaction of API with excipients, container closure systems and packaging materials.

Stress testing

As outlined in the SADC stability guideline/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 recognized pharmacopoeia for the API or FPP, it is sufficient to state "protect from light" on labelling, in lieu of photostability studies, when the container closure system is shown to be light protective. Additional stress testing of specific types of dosage forms may be appropriate (e.g. cyclic studies for semi-solid products, freeze-thaw studies for liquid products).

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

Stability data must demonstrate stability of the medicinal product throughout its intended shelf-life under the climatic conditions prevalent in the target countries. Merely applying the same requirements applicable to other markets could potentially lead to substandard products, e.g. stability studies conducted for countries in Climatic Zone I/II when the products are supplied in Namibia with Climatic Zones IV. Refer to WHO Technical Report Series, No. 953, Annex 2, Appendix 1 for information on climatic zones. The required long-term storage conditions are 30°C±2°C/75% ± 5%RH, and the long-term data submitted in the PD (see table below) should be at these conditions. The use of alternative long-term conditions will need to be justified and should be supported with appropriate evidence.

Other storage conditions are outlined in the SADC stability guideline/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.

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

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

*Where long-term conditions are 30°C±2°C/75% ± 5%RH, there is no intermediate condition. Where stability conditions for long term studies are done at 25°C±2°C/60%RH, the applicant should make a commitment to conduct studies at recommended 30°C±2°C/75%

Refer to WHO Technical Report Series, No. 953, Annex 2 for further information regarding the storage conditions.

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

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

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

The information on the stability studies should include details such as

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

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as “all tests meet specifications”. This should include ranges of analytical results and any trends that were observed. For quantitative tests (e.g. individual and total degradation product tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements such as “within limits” or “conforms”. Dissolution results should be expressed at minimum as both the average and range of individual results.

Applicants should consult ICH’s Q1E guideline for details on the evaluation and extrapolation of results from stability data (e.g. if significant change was not observed within 6 months at accelerated condition and the data show little or no variability, the

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

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

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

Reference ICH Guidelines: Q1A, Q1B, Q1C, Q1D, Q3B, and Q5C, Q6A, WHO Technical Report Series, No. 953, Annex 2

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 PD, 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 in every strength and every container closure system, if relevant, should be included in the stability programme (unless none is produced during that year). Bracketing and matrixing may be applicable. A written commitment (signed and dated) to this effect should be included in the dossier.

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

Reference ICH Guidelines: Q1A and Q5C

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

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

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

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

Reference ICH Guidelines: Q1A, Q1B, Q1C, Q1D, Q1E, Q2A, Q2B and Q5C

3.2.A APPENDICES

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

Biotech:

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

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

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

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

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

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

<u>For non-viral adventitious agents:</u>

Detailed information should be provided on the avoidance and control of non-viral

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

Reference ICH Guidelines: Q5A, Q5D, and Q6B

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

<u>Materials of Biological Origin</u>
Information essential to evaluate the virological safety of materials of animal or human origin (e.g. biological fluids, tissue, organ, cell lines) should be provided. (See related information in 3.2.S.2.3, and 3.2.P.4.5). For cell lines, information on the selection, testing, and safety assessment for potential viral contamination of the cells and viral qualification of cell banks should also be provided. (See related information in 3.2.S.2.3).

<u>Testing at appropriate stages of production</u>
The selection of virological tests that are conducted during manufacturing (e.g., cell substrate, unprocessed bulk or post viral clearance testing) should be justified. The type of test, sensitivity and specificity of the test, if applicable, and frequency of testing should be included. Test results to confirm, at an appropriate stage of manufacture, that the product is free from viral contamination should be provided. (See related information in 3.2.S.2.4 and 3.2.P.3.4).

<u>Viral Testing of Unprocessed Bulk</u>
In accordance with Q5A and Q6B, results for viral testing of unprocessed bulk should be included.

<u>Viral Clearance Studies</u>
In accordance with Q5A, the rationale and action plan for assessing viral clearance and the results and evaluation of the viral clearance studies should be provided. Data can include those that demonstrate the validity of the scaled-down model compared to the commercial scale process; the adequacy of viral inactivation or removal procedures for manufacturing equipment and materials; and manufacturing steps that are capable of removing or inactivating viruses. (See related information in 3.2.S.2.5 and 3.2.P.3.5).

Reference ICH Guidelines: Q5A, Q5D, and Q6B

3.2.A.3 Excipients

3.2.R REGIONAL INFORMATION

3.2.R.1 Pharmaceutical and Biological availability

SCOPE

This module addresses the pharmaceutical and biological availability for multisource applications and NCE line extensions with special reference to the purpose of the study (ies), the reference product(s) and the overall conclusion.

i) Partial exemption from the requirements of 3.2.R.1 and 5.3.1 may be applicable if efficacy and safety are intended to be established by clinical data (or for other reasons as determined by the Council), provided that clinical trials have been conducted with the same formulation as the one being applied for, in which case
   - the pharmaceutical availability profile(s) of the API(s) in the final formulation being applied for, for which exemption or partial exemption is justified, should specifically be demonstrated, e.g. the dissolution profiles for solid oral, oral suspension and parenteral suspension products should be included in accordance with the Dissolution guideline, and/or other relevant data provided to unequivocally characterise the formulation used in the clinical trials.

ii) If clinical evidence in support of efficacy is not submitted, or if the final formulation being applied for is not the same as that used in clinical trials, studies and data to demonstrate the pharmaceutical and/or biological availability / equivalence of the product should be included.

iii) If in the opinion of the applicant no data are required to substantiate efficacy (e.g. parenteral solutions) clearly state the rationale for accepting safety and efficacy and include a discussion on the excipients (refer Bioavailability/Bioequivalence guideline section 4), and a comparison of final product characteristics in 3.2.R.1.4.2.

iv) One of the following methods depending on the relevancy may be used
   - Bioavailability
   - Dissolution
   - Disintegration
   - Acid neutralising capacity
   - Microbial growth inhibition zones
   - Proof of release by membrane diffusion
   - Particle size distribution
   - Blanching test
   - Any other method provided the rationale for submitting the particular method is included.

v) Data submitted should always be comparative, except as stated under 3.2.R.1 I i) when product characterisation is submitted.

a) Bioequivalence and/or biowaivers

Refer to the Bioavailability/bioequivalence guideline as well as the Annex I for the dissolution requirements.

b) In vitro dissolution
The studies should be carried out in accordance with the Annex I for the dissolution requirements.

c) Disintegration
Disintegration as proof of efficacy may be used in the following instances:
- Vitamins or vitamins and mineral combinations when a claim is made as a supplement.
- Sucralfate.

The disintegration test included for Nutritional Supplements in the USP, or in the Ph Eur should be used for the vitamins. The general disintegration test included in the USP/Ph Eur may be used for the other substances.

d) Acid neutralising capacity

Acid neutralising capacity may be used as proof of efficacy for products with an antacid or acid neutralising claim. The acid neutralising capacity test included in the USP should be used.

e) Microbial growth inhibition zones

Microbial growth inhibition zones may be used as proof of efficacy for simple solution topical formulations with a bacteriostatic/bacteriocidal/antiseptic claim.

f) Proof of release by membrane diffusion

Proof of release by membrane diffusion will not be accepted as proof of efficacy alone, unless data are presented that show a correlation between release through a membrane and clinical efficacy.

g) Particle size distribution

Particle size distribution may be used in support of proof of efficacy for inhalations. The Anderson sampler or equivalent apparatus should be used. In addition appropriate information should be submitted to provide evidence of clinical safety and efficacy.

h) Blanching test

The blanching test may be used as proof of efficacy for topical dosage forms containing topical corticosteroids.

The rationale for any other particular method should be provided.

STUDY PRODUCTS

A sufficient number of retention samples of both test and reference products used in the bioequivalence or other studies, should be kept for one year in excess of the accepted shelf-life, or two years after completion of the trial or until approval, whichever is longer, in order to allow re- testing if so required by the NMRC.

A complete audit trail of procurement, storage, transport and use of both the test and reference products should be recorded.

1) Batch Size

The batch used in the bioequivalence or other studies should satisfy the following requirements:

(i) The batch size should be a minimum of 100 000 units or at least 10 % of the production batch, whichever is greater. If the batch size is less than 100 000 units, the use of a smaller batch size should be motivated/justified.

(ii) If the production batch size is smaller than 100 000 units, a full production batch should be used.

(iii) A high level of assurance should be provided that the product and process used in the production of the product will be feasible on an industrial scale. If the product is subjected to further scale-up, this should be validated appropriately.

2) Reference Products (comparators)

Copies of the labelling (label(s) and package insert) for the reference/innovator product should be provided in 3.2.R.1.2

If a different chemical form is used, it must be confirmed that the safety / efficacy profile is not altered (3.2.R.1.1.11). The confirmation may be documented / bibliographical evidence. If well known (e.g. hydrochloride, maleate, nitrate, stearate), reference to a pharmacopoeia accepted by NMRC may be acceptable.

a) Selection of Reference Product

The reference product should be an innovator product registered by Council and should be preferably procured in Namibia or from the following countries or regions – SA, US, EU, Australia, Canada, and Japan. An exception is an “OLD MEDICINE” that may be used as a reference product when no other such product has been registered provided that it is available on the market in Namibia or countries listed above. If more than one such product is available the market leader should be used as the reference (e.g. IMS database). Applicant has to submit evidence to substantiate market leadership claim.

The following options for selection of the reference product are listed in order of preference:

(i) the innovator product registered and procured in Namibia; or

(ii) the innovator product, registered in Namibia, for which a marketing authorization has been granted by the health authority of a country recognized by the NMRC (SA, US, Canada, EU, Australia & Japan), in which the product is listed as reference listed drug, and which is to be purchased from that market, or

(iii) a product from the latest edition of the WHO International comparator products for equivalent assessment of interchangeable multisource (generic) products QAS/05.143. [http://www.who.int/medicines/services/expertcommittees/pharmprep/QAS05_143_Comparator] The primary manufacturing site is indicated in the WHO comparator list, and the comparator is to be purchased in that country, or;

(iv) in the case that no innovator product can be identified – within the context of (i)–(iii) above, the choice of the reference must be made carefully and must be comprehensively justified by the applicant.

b) Reference Products for Combination Products

Combination products should, in general, in accordance with a) above, be assessed with respect to bioavailability and bioequivalence of individual active substances:

- Either single entity products administered concurrently (in the case of clinically justifiable combinations), or
- Using an existing combination as the reference, which should be an innovator product registered by the NMRC or regulatory authorities in countries recognized by NMRC on safety and efficacy data.

In the former instance, immediate release oral dosage forms containing a single API may be used as the reference. These reference products may include “OLD MEDICINES”.

3.2.R.1.1 Overview

3.2.R.1.1.1 Country where developed, company developed by, test product synonyms.
Give a brief introductory description of the development of the test product, the innovator and test product synonyms

3.2.R.1.1.2 The type of study(ies) submitted as proof of efficacy, i.e. bioequivalence, dissolution, comparative dissolution or other study(ies)
Give a brief description of the rationale for the different studies.

3.2.R.1.1.3 The purpose of the study or studies (more than one may be applicable)

1) comparison of the formulation to be marketed versus the formulation used in clinical trials, or
2) proof of efficacy for a multisource (generic) new dosage form/new strength medicine application, or
3) proof of efficacy of new formulation (formulation change); or
4) proof of efficacy of products manufactured by new manufacturer (manufacturer different to that of the test product - or previously approved/registered - when relevant as per the Amendments guideline); or
5) biowaiver in accordance with:
   - Similarity (for additional strengths)
   - Biopharmaceutical Classification System (BCS)
6) characterisation of the clinical trial(s) test product being applied for.

3.2.R.1.1.4 The status of the reference product

- Clinical trial formulation
- Innovator product
- Current formulation (for change of formulation)

3.2.R.1.1.5 A description of the type of study(ies), bioequivalence, dissolution, comparative dissolution or other study(ies)

3.2.1.1.6 Confirmation that the data submitted have been obtained with the formulation and manufacturing process being applied for.

If the formulation and or manufacturing process being applied for is different to that of the test product the relevant requirements in accordance with the Amendments guideline should be complied with and the relevant dissolution, stability and validation data included in 3.2.R.1.4, 3.2.P.8 and 3.2.P.3.5 respectively.

Studies five years and older:
Submit data to confirm that the product being applied for is identical to the test product used in the bioequivalence study. The data should include but not be limited to the following:

- Unit formulation, manufacturing procedure and equipment
- Site of manufacture of final product and manufacturer of the API
- Overall product specifications and
- Other relevant information

3.2.R.1.1.7 Confirmation that the test product (all strengths) was manufactured by the same manufacturer and site applied for.

If the manufacturer or site being applied for is different to that of the test product the relevant requirements in accordance with the Amendments guideline should be complied with and the dissolution, stability and validation data included in 3.2.R.1.4, 3.2.P.8 and 3.2.P.3.5 respectively.

3.2.R.1.1.8 Confirmation that the test product was manufactured with API(s) manufactured by the same API manufacturer as being applied for.

Proof of physico-chemical equivalence is required if the manufacturer of the API is additional or different to that stated in 3.2.S and must be included in 3.2.R.4. The relevant requirements in accordance with the Amendments guideline should also be complied with and the dissolution, stability and validation data included in 3.2.R.1.4, 3.2.P.8 and 3.2.P.3.5 respectively.

3.2.R.1.1.9 A statement whether in vivo-in vitro correlation from the data was obtained by the method/s used, if applicable.

In vivo-in vitro correlation data should be included in 5.3.1.3

3.2.R.1.1.10 Motivation for the use of the particular reference product [Refer to Selection of Reference Products II (2) above]

The applicant should justify the choice of reference product.

Proof of country of origin for reference product (proof of purchase)
The following additional information should be supplied for the reference product used in biostudie(s):

i. The name and address of the manufacturing site where the reference product is manufactured.
ii. The qualitative formulation of the reference product.
iii. Copies of the immediate container label as well as the carton or outer container label of the reference product.
iv. For modified release, evidence of the mechanism of modified release of the reference product.
v. The method of manufacture of the reference product if claimed by the applicant to be the same.
vi. Procurement information of the reference product
    - Copy of licensing agreement/s if relevant
    - Distribution arrangements / agreement/s if relevant
    - Copy of purchase invoice (to reflect date and place of purchase) 3.2.R.1.2
    - Proof of shipment in form of airway bill
    - Proof of storage conditions from time of purchase to time of study initiation

3.2.R.1.1.11 Motivation for the use of a pharmaceutical alternative or lower strength

3.2.R.1.1.12 Tabular summary of the information pertaining to the study products

To facilitate evaluation a tabular summary (example on the next page) of the following information pertaining to the study products, is required.

1. Full details of the reference product(s) used as the standard for reference purposes (including e.g. the applicant, proprietary name, lot number, expiry date).
2. If the reference product is registered but not procured in Namibia, the labelling / SPC / Package insert of the reference product translated into English if not in English.
3. Full details of the test product (including e.g. the applicant, proprietary name, lot number, expiry date).
4. Assay of test and reference products. The assay of the test and reference products should not differ by more than 5 % in assay unless justified.
5. Dissolution profiles of test and reference products (Annex I on comparative dissolution studies)
6. Certificates of Analysis for the test and reference products, analysed

using the control procedures for description, assay, content uniformity and dissolution proposed in the submission for the test product. Include in 3.2.R.1.3

7. A CoA of the API used in the test product study-batch.
8. The size of the study/test product batch.

Tabular summary of study products

Example may be adapted as appropriate. Extra rows may be included as required to reflect e.g. more detailed dissolution results or similarity factors values, or page numbers of documents.

Product information	Reference product(s)	Test product formulation applied for
Name		
Biostudy Batch no and expiry date		
HCR/PHCR		
Country where purchased		***
Manufacturing site		
Assay results *		
Dissolution results		
Comparative dissolution Batch no and expiry date		
Assay results %		
Comp. dissolution results		
Similarity f2		
Source of API	If known/relevant	**
Batch size	If known/relevant	
Product status	Clinical trial formulation Or innovator product or current formulation as the case may be	
CoA, test and reference products and API of test product study batch	3.2.R.1.3p	3.2.R.1.3p
Package insert	3.2.R.1.2p	Module 1.3
Label	3.2.R.1.2 p	Module 1.3
*Justification if the difference between test and reference is more than 5% ** Proof of physical / chemical equivalence is required if the manufacturer is different to that in 3.2.S **** Motivation and supporting data are required if the manufacturer and/or the site applied for is different to the manufacturer and/or site of the test product		

3.2.R.1.1.13 The formulation of each of the dosage strengths of the test product(s) in tabular form in the case of a an application for a biowaiver of proportionally similar dosage strengths

3.2.R.1.1.14 A discussion and conclusion of the outcomes of each of the studies and other relevant information to support and justify acceptance of product efficacy

3.2.R.1.1.15 An overall conclusion

It is important to include, in addition to the individual study conclusions, an overall conclusion of all the data submitted to support and justify product efficacy and where relevant, safety.

3.2.R.1.1.16 References

3.2.R.1.2 Reference product/s (local and foreign) (identification/documentation)

- Package inserts
- label and carton,
- qualitative formulation,
- proof of procurement/invoice (foreign product)

3.2.R.1.3 Certificates of Analysis

1) Biostudy reference product
2) Biostudy test product and any other strength
3) API of the test product
4) Before and after formulation/manufacturer/API changes

3.2.R.1.4 Pharmaceutical availability studies

3.2.R.1.4.1 Dissolution studies, data and reports

1) Dissolution profiles of the test and reference products. This information should be submitted as part of pharmaceutical development studies (refer section 3.2.P.2.2.1).
2) Comparative dissolution between different strengths of the test product (biowaiver of additional strengths). The appropriate form should be completed and data submitted in section 5.3.1.2
3) Comparative dissolution between test and reference products (BCS biowaiver). The appropriate form should be completed and data submitted in section 5.3.1.2.
4) Comparative dissolution data in support of:
   - additional or different API manufacturer
   - additional or different FPP manufacturer and/or site
   - different formulation

   being applied for to that of the test product.

3.2.R.1.4.2 1) Other

2) Motivation for exemption of data to substantiate efficacy.

If in the opinion of the applicant no data are required to substantiate efficacy (e.g. parenteral solutions) the rationale for accepting safety and

efficacy should be clearly stated and include a discussion on the excipients (refer bioavailability/ bioequivalence guideline), and comparison of final product characteristics.

3.2.R.2 Parent API manufacturer with various sites

If an identical route of synthesis, or manufacturing process of the PPL (in case of Biological Medicines), including the purification step is used by each site of the same parent company, a statement to this effect will suffice with regard to the route.
In this case include valid CoAs from the API manufacturer or manufacturer of the primary production lot (in case of Biological Medicines) for two batches issued by each site.

3.2.R.3 Certificate(s) of suitability with respect the Ph.Eur. (CEPs)

A valid EU certificate of suitability (CEP) may be submitted if available. The CEP certifies the suitability of the relevant Ph. Eur. monograph to control the quality of the API produced by the manufacturer specified in the CEP. The Ph. Eur. must be used for API specifications and procedures if a CEP is submitted.

Please ensure that any annexes mentioned in the CEP accompany the CEP. Any additional requirements indicated in the CEP and the methods described in the annexes are officially part of the API specification. Also ensure that the declaration of access is completed. If a CEP is submitted, detailed description of the methods of synthesis and analysis of the API are not required.

Impurities and residual solvents listed in the CEP should be included in the API specifications (3.2.S.4.1). It is the responsibility of the applicant to be aware of changes in the status of CEPs that are used for their products and to notify Council accordingly. It is also the responsibility of the applicant to ensure that the revised CEP is obtained from the CEP holder when applicable and to submit such updated CEP. If the CEP is withdrawn or suspended for whatever reason a DMF or APIF should be submitted within six months, in accordance with 3.2.S. The validity of the CEP can be verified under “Certification” at: http://www.edqm.eu/site/Databases-10.html

In addition:

a) Any information required for the APIF but not addressed in the CEP must be submitted, e.g. physico-chemical properties [3.2.S.1.3 above].
b) If the retest period is not reflected in the CEP, stability data generated according to the Stability guideline and/or supporting literature to demonstrate the API stability should be submitted. (Module 3.2.S.7)
c) Certificates of Analysis (CoAs) from the API manufacturer relating to at least two batches should be included. (Module 3.2.S.4.4)

3.2.R.4 Multiple API manufacturers

If more than one manufacturer of the API is being applied for (irrespective of the apparent similarity of the routes utilised by the different manufacturers), or when different routes of synthesis are used in the manufacture of the API, the following should be submitted, in addition to Module 3.2.S for each API:

3.2.R.4.1 Comparative API manufacturers study report

A report pointing out the differences in the routes used, where applicable, and the differences with regard to the impurity profiles and residual solvents unless justified. The specifications for the API from the FPP manufacturer should make provision for these impurities and residual solvents.

3.2.R.4.2 Comparative results

A report, signed and dated, is required addressing the following:

For more than one manufacturer of the API comparative critical tests, e.g. identification, assay, solubility and/or dissolution, particle size distribution, polymorphism, optical rotation, residual solvents and impurity profiles, to demonstrate physical and chemical equivalence, should be performed on a sample from each API manufacturer by the same laboratory (either the laboratory of the manufacturer or an independent laboratory).

The same analytical methods and equipment should be used for these tests.

These results should be presented also in tabular format and spectra should preferably be overlaid.

3.2.R.4.3 Confirmation of compliance with guidelines

Confirmation of compliance with the Amendments guideline, stating type and category, and identification of the location of the relevant data in the dossier is required

Confirmation of compliance with the Stability guideline and identification of the relevant data in the dossier is required.

3.2.R.4.4 Certificates of analysis

Provide certificates of analysis for each batch of API reported on in 3.2.R.4.2

3.2.R.5 Medical device

3.2.R.6 materials of animal and / or human origin

All ingredients of animal origin (excluding products from porcine origin) should be BSE/TSE free.

Include a declaration from FPP manufacturer that the materials used will always comply with BSE/TSE free requirements.

3.2.R.7 Production documentation

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

3.2.R.7.1 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.

3.2.R.7.2 Master production documents

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

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

a) master formula;
b) dispensing, processing and packaging sections with relevant material and operational details;
c) relevant calculations (e.g. if the amount of API is adjusted based on the assay results or on the anhydrous basis);
d) identification of all equipment by, at minimum, type and working capacity (including make, model and equipment number, where possible);
e) process parameters (e.g. mixing time, mixing speed, milling screen size, processing temperature range, granulation end-point, tablet machine speed (expressed as target and range));

f) list of in-process tests (e.g. appearance, pH, assay, blend uniformity, viscosity, particle size distribution, LOD, weight variation, hardness, disintegration time, weight gain during coating, leaker test, minimum fill, clarity, filter integrity checks) and specifications;
g) sampling plan with regard to the:
    i. steps where sampling should be done (e.g. drying, lubrication, compression),
    ii. number of samples that should be tested (e.g. for blend uniformity testing of low dose FPPs, blend drawn using a sampling thief from x positions in the blender),
    iii. frequency of testing (e.g. weight variation every x minutes during compression or capsule filling);
h) precautions necessary to ensure product quality (e.g. temperature and humidity control, maximum holding times);
i) for sterile products, reference to SOPs in appropriate sections and a list of all relevant SOPs at the end of the document;
j) theoretical and actual yield;
k) compliance with the GMP requirements.

Reference documents: WHO Technical Report Series, No. 961

3.2.R.8 Analytical procedures and validation information

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

3.3 LITERATURE REFERENCES

Key literature referenced should be provided, if applicable.

MODULE 4: NON CLINICAL STUDY REPORTS

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

For detailed information and guidance on information for new medicines, the human study reports and related information should be presented in the order described in ICH M4S.

Generally, module 4 is not applicable for well-known active pharmaceutical ingredients (generic medicines).

MODULE 5: CLINICAL STUDY REPORTS

Module 5 of the dossier contains the clinical data relevant to the application. In most circumstances, the clinical studies included in Module 5 of the dossier will be

international studies used to establish the pharmacodynamics, pharmacokinetics, safety and efficacy of the medicine across an international patient population. However, where there is evidence to suggest that the pharmacokinetics or pharmacodynamics of the product may vary across the populations that will use the medicine in Namibia, the sponsor should consider submitting studies relevant to those target populations.

For detailed information and guidance on presentation of information for new medicines, the human study reports and related information should be presented in the order described in ICH M4E.

The majority of applications for well-known active pharmaceutical ingredients (generic medicines) are supported by one or more pivotal comparative bioavailability studies. When filing an application in the CTD format, it is anticipated that only the following relevant sections of Module 5 will normally be required for these generic medicines.

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

Partial or total exemption from the requirements of Module 5.3.1 may be applicable if efficacy and safety are intended to be established by clinical data (or for other reasons as determined by the Council), provided that clinical trials have been conducted with the same formulation as the one being applied for.

To justify exemption from the requirements of Module 5.3.1 it should be clearly stated and confirmed:

- that clinical trials have been performed with the formulation being applied for in Module 3.2.P1 and
- that the regional requirements of 3.2.R.1 Pharmaceutical and Biological Availability have been addressed.

If clinical evidence in support of efficacy is not submitted, or if the final formulation being applied for is not the same as that used in clinical trials, refer 3.2.R.1 Pharmaceutical and Biological Availability.

5.3.1.1 Bioavailability (BA) study reports

5.3.1.2 Comparative bioavailability and bioequivalence study reports

For further guidance on bioavailability/ bioequivalence or biowaiver applications, the applicant should refer to the SADC guidelines for Bioavailability/Bioequivalence guidelines

5.3.1.3 In vitro–in vivo correlation study reports if available

5.3.1.4 Reports of bioanalytical and analytical method for human studies

For further guidance on bioavailability/ bioequivalence or biowaiver applications, the applicant should refer to the SADC guidelines for Bioavailability/Bioequivalence guidelines and European Medicines Agency Guideline on Bioanalytical Method Validation.

5.3.7 Case-report forms (CRFs) and individual patient listings:

For clinical efficacy and safety studies: Only CRFs for subjects who experienced serious adverse events should be included. All CRFs should be available upon request.

For bioequivalence studies: all CRFs for all subjects should be submitted (refer to Bioavailability / bioequivalence guideline for more information)

5.4 Literature references

References to the scientific literature relating Module 5 should be included in this section of the PD when appropriate.

REFERENCES

1. Commission regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food.
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4. Common technical document for the registration of pharmaceuticals for human use – quality questions & answers/location issues. European Medicines Agency, 2009 (http://www.ema. europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002726.pdf).
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14. 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).

15. Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-sixth report. Geneva, World Health Organization, 2012, Annex 4 (WHO Technical Report Series, No. 970).
16. ICH Guidelines (Q1 Stability; Q2 Analytical validation; Q3A, Q3B, Q3C Impurities; Q5 Biotechnological Products; Q6A, Q6B Specifications; Q7 GMP for APIs, Q8 Pharmaceutical Development; Q9 Quality Risk Management; Q10 Pharmaceutical Quality System)
17. ICH harmonised tripartite guideline: the common technical document for the registration of pharmaceuticals for human use: quality – M4Q. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2002.
18. Inactive ingredient guide. US Food and Drug Administration, http://www.accessdata.fda.gov/ scripts/cder/iig/index.cfm
19. 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).
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APPENDIX 1 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). The 15-minute time-point is critical to determine whether a product is very rapidly dissolving and to determine whether f_2 must be calculated. For extended-release FPPs, the time-points should be set to cover the entire duration 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 media covering the physiological range, including pH 1.2 hydrochloric acid, pH 4.5 buffer and pH 6.8 buffer. International Pharmacopoeia buffers are recommended; other pharmacopoeial buffers with the same pH and buffer capacity are also accepted. Water may be considered as an additional medium, especially when the API is unstable in the buffered media to the extent that the data are 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 (f_2): $f_2 = 50 \text{ LOG } \{[1+1/n \sum^{n}_{t=1} (R_t - T_t)^2]^{-0.5} \times 100\}$ where R_t and T_t are the mean per cent API dissolved in reference (comparator) and test product, respectively, at each time-point. An f_2 value between 50 and 100 suggests that 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 determination of each profile. Mean dissolution values can be used to estimate the similarity factor, f_2. To use mean data, the percentage coefficient of variation at the first time-point should be not more than 20% and at other time-points should be not 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.
- 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 the absence of surfactant should be provided. The rationale for the choice and concentration of surfactant should be provided. The concentration of the surfactant should be such that the discriminatory power of the test will not be compromised.

APPENDIX 2 PRODUCT QUALITY REVIEW REQUIREMENTS FOR ESTABLISHED MULTISOURCE PRODUCTS

For an established multisource product, a product quality review may satisfy the requirements of sections 3.2.P.2.2.1 (a), 3.2.P.2.3 (a) and 3.2.P.3.5 of the PD and QOS-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 no fewer than 10 consecutive batches manufactured over the period of the past 12 months or, where 10 batches were not manufactured in the past 12 months, no fewer than 25 consecutive batches manufactured over the period of the past 36 months and should include at least:

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

Notes

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

Data should be presented in tabular or graphical form, when applicable.

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

LIST OF ACRONYMS

API	Active Pharmaceutical Ingredient
APMF	Active Pharmaceutical Ingredient Master File
BCS	Biopharmaceutics Classification System
BP	British Pharmacopoeia
BSE	Bovine Spongiform Encephalitis
CEP	European Certificate of Suitability
cGMP	Current Good Manufacturing Practices
CoA	Certificate of Analysis
CTD	Common Technical Document
CV	Curriculum Vitae
DMF	Drug Master File
DSC	Differential Scanning Calorimetry
EMA	European medicines Agency
EU	European Union
FDA	US Food and Drug Administration
FDC	Fixed Dose Combination
FPP	Finished Pharmaceutical Product
FPRC	Final Product Release Control
FPRR	Finished Product Release Responsibility
GC	Gas Chromatography
GMP	Good Manufacturing Practices
HPLC	High Performance Liquid Chromatography
ICH	International Conference on Harmonisation
INN	International Non-proprietary Name
IPI	Inactive Pharmaceutical Ingredient
IR	Infrared
MDD	Maximum Daily Dose
MS	Mass Spectra
NCE	New Chemical Entity
NMRC	Namibia Medicines Regulatory Council
NMRT	Nuclear Magnetic Resonance
NMT	Not More Than
PD	Product Dossiers
Ph Eur	European Phamacopoeia
QA	Quality Assurance
QOS	Quality Overall Summary
TLC	Thin Layer Chromatography
TSE	Transmissible Spongiform Encephalopathy
USP	United States Pharmacopoeia
UV	Ultraviolet
VP	Validation Protocol
VR	Validation Report
WHO	World Heath Organization
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 mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form, and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body.

Active pharmaceutical ingredient (API) starting material

A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house (ICH Q7). See also starting materials for synthesis.

Applicant

The person or entity that is responsible for submitting an application for registration of a medicine to the Namibia Medicines Regulatory Council

Biopharmaceutics Classification System (BCS) highly soluble

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

Commitment batches

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

Comparator product

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

based on the information presented under Guidance on bioequivalence studies available on the Prequalification web site.

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, which has been previously approved through a finished product by a stringent regulatory authority or by WHO, but requires the filing of a dossier. This would include, for example, new PDs and variations to multisource products..

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.

Inactive pharmaceutical ingredient (IPI)

A substance or compound that is used in the manufacture of a pharmaceutical product and does not contribute to the therapeutic effect of the product, but is intended to enhance the consistency, appearance, integrity, stability, release characteristics, or other features of the product.

Innovator pharmaceutical product

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

Manufacturer

A company that carries out operations such as production, packaging, repackaging, labelling and relabelling 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.

Officially recognized pharmacopoeia (or compendium)

Those pharmacopoeias recognized by the NMRC (i.e. British Pharmacopoeia (BP),

European Pharmacopoeia (Ph.Eur.), The International Pharmacopoeia (Ph.Int.), Japanese Pharmacopoeia (JP) and 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. For the WHO Prequalification of Medicines Programme, 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 API master file (APIMF). A starting material for a synthetic API is a chemical compound of defined molecular structure that contributes to the structure of the API. See also API starting material.