MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

PHARMACEUTICAL AND ANALYTICAL
CTD /eCTD

This guideline is intended to provide recommendations to applicants wishing to submit applications for the registration of medicines. It represents the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. Council reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine in keeping with the knowledge current at the time of evaluation. Alternative approaches may be used but these should be scientifically and technically justified. The MCC is committed to ensure that all registered medicines will be of the required quality, safety and efficacy. It is important that applicants adhere to the administrative requirements to avoid delays in the processing and evaluation of applications.

Guidelines and application forms are available from the office of the Registrar of Medicines and the website.

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REGISTRAR OF MEDICINES
MS M HELA

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The requirements for pharmaceutical and analytical information are divided into three modules in the CTD, i.e. Module 2.3 (CTD Quality Overall Summary), Module 3 (Quality) and Module 5.3.1 (Reports of Biopharmaceutic Studies).

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5.3 Clinical study reports

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The above Modules should be read together with the following pharmaceutical and analytical related guidelines:

Alcohol Content of Medicines

Post-Importation Testing

Stability

Biostudies

Dissolution

Amendments

The SA GMP guideline e.g. Chapter 4 for Documentation and

Annex 15 of the SA GMP guideline regarding Validation.

For NCEs the ICH guidelines also apply.

For Biological Medicines the ICH, WHO and EMA guidelines also apply where appropriate.

In accordance with Section 2 of Module 1.1of the Guidance for the submission of the CTD, each Module must include a Table of Content (ToC) under the first section of the Module.

Refer to Biostudies guideline 3.9 for the (ToC) requirements of Module 5.3

Shading in tables should be avoided as this could render text illegible when photocopied.

If the application is being submitted simultaneously with one or more additional applications for the identical product this should be stated and also confirmed that the submissions are identical except for the proprietary name, in the application form in Module 1.2.1. This information should also be included clearly in the covering letter of each product.

2 MODULE 2 - CTD SUMMARIES

2.3 Quality Overall Summary- Introduction

2.3.S Quality Overall Summary - Active Pharmaceutical Ingredient (name, manufacturer)

2.3.P Quality Overall Summary - Finished Pharmaceutical Product (name, dosage form)

2.3.A Quality Overall Summary - Appendices

The Quality Overall Summary (QOS) should include sufficient information to provide the reviewer with an overview of Module 3. The QOS should also emphasise critical key parameters of the API and product, for instance, justification in cases where guidelines were not followed.

3 MODULE 3 - QUALITY

3.1 Table of contents of Module 3

3.2 Body of data

3.2.S Active Pharmaceutical Ingredient *(name, manufacturer)*

Neither the complete nor the open part of the DMF should be sent directly to the MCC.

The information should be submitted in the dossier under the following headings below.

The documentation must comply with the SA Guide to GMP Chapter 4 Requirements for Documentation including at least unique identification, version and date. A declaration that it is current must be included.

Starting materials for in situ API preparation are treated as APIs.

For a mixture of API(s) or API(s) with (IPIs), the blending of the ingredients is considered as the first step in the manufacture of the final product, and therefore does not fall under the definition of an API even though it may take place in a different facility. The resultant mixture, or partially completed final product e.g. coated or uncoated granules, is regarded as an FPP intermediate.

The only exceptions can be made where the API cannot exist on its own, e.g. due to insufficient stability without a stabilising agent. Examples from the Ph.Eur. include: dihydrostreptomycin sulphate, moxidectin and streptomycin sulphate.

The mixing of the API with an IPI or another API thus forms part of the manufacturing procedure of the final product which is addressed in Module 3.2.P.3 whilst the API(s) used in such mixtures should be included in Module 3.2.S, according to the requirements of Modules 3.2.S.1 to 3.2.S.7 and 3.2.R.6. The formulation, API and IPI specifications and control procedures, packaging materials, stability and pharmaceutical development of the FPP intermediate are addressed in Modules 3.2.P.3; 3.2.S.2; 3.2.P.4; 3.2.P.7; 3.2.P.8 and 3.2.P.2 respectively in accordance with the requirements of the relevant Modules.

In case of blood fractions a Plasma Master File (PMF) should be included in the dossier.

A separate 3.2.S should be submitted:

- for each API (in case of a fixed dose combination product),
- for each API manufacturer applied for
- for those sections that are relevant to the FPP manufacturer in terms of testing of the API, e.g. 3.2.S.4

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

3.2.S.1.1 Nomenclature *(name, manufacturer)*

The approved name, or International Non-proprietary Name (INN), or chemical description of the API(s), should be stated.

The approved name should be the same as the name reflected in Module 1.3

3.2.S.1.2 Structure *(name, manufacturer)*

The structural formula (indicating stereochemistry where appropriate), systematic name, the empirical formula and the relative molecular mass should be stated.

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

The physical and chemical properties of the API, including e.g. solubility, particle size, hygroscopicity should be indicated.

3.2.S.1 General information (name, manufacturer) - 3.2.S.1.3 continued

The solubility of each API should be stated in terms of a unit part of the substance per number of parts of the solvent, or in unit mass of substance in a given volume of solvent, at a specific temperature. The solvents should include water and the solvent(s) relevant to the product formulation.

If the API has a low solubility in water in accordance with the BCS definition the solubility should be quantified (mg/ml).

Evidence of occurrence of isomers, chirality and polymorphism, where applicable, should be provided. The absence of isomers, chirality and/or polymorphism should be confirmed.

For a multisource product the API must be identical in structure and stereochemistry to the API used as the reference product (pharmacopoeial structure).

3.2.S.2 Manufacture *(name, manufacturer)*

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

The name, business and physical address of each manufacturer of the API being applied (including any intermediate manufacturer) should be stated.

No API from any manufacturer, other than the approved manufacturer(s), may be used.

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

A short description of the synthesis and a flow chart which includes the structures and stereochemistry of starting materials and intermediates; reagents, catalysts, solvents, isolation and purification; and any other relevant aspects. Note that specifications and control procedures for substances used in this process are not generally required. (The specific processes carried out by any intermediate manufacturer should be identified.)

Other relevant aspects, e.g. preparation of sterile material (full description of aseptic or sterilisation process including conditions), if there is no further sterilisation of the FPP.

See 3.2.R.3 below for alternative to this section.

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

(1) Full details of tests and specifications for pharmaceutical ingredients used in the production of the primary production lot should be provided. (Refer to WHO guidelines on Biologicals).

(2) In the case of biological medicines produced using the cell bank or seed lot system, the history (origin and sources) and preparation of the seed lot and or cell lines should be described with specific reference to the tests that are carried out on such a seed lot or cell bank to establish and maintain the integrity thereof (EMA and or WHO guidelines).

(3) Particulars of the composition of all culture media used in the preparation and testing of a biological medicine should be given. All raw materials of animal or human origin must be specified as well as suppliers (indicating the country of origin) and the CoA.

(4) Particulars should be given of the other biological source material from which a biological medicine (e.g. blood fractions) is extracted, including the origin of the culture or blood.

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

Submit information relevant for the FPP manufacturer e.g. sterile material.
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.

Reference ICH Guidelines: Q6A and Q6B

Additionally for Biotech: Stability data supporting storage conditions should be provided – Reference ICH Guideline Q5C

3.2.S.4 Control of active pharmaceutical ingredient (name, manufacturer) - continued

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

Provide full validation data on the aseptic processing and sterilisation process where there is no further sterilisation of the FPP.

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

For NCEs refer to ICH M4Q.

3.2.S.3 Characterisation *(name, manufacturer)*

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

Provide structure (including stereochemistry) elucidation for new chemical entities (NCEs).

Proof of correctness of structure for a well-known API, e.g. IR spectrometric comparison against an official standard may be acceptable. In the case of enantiomers an additional test is required to confirm its identity (pharmacopoeial).

If the API is not described in a monograph of any of the official pharmacopoeias, no official standard is available in which case sufficient evidence (NMR, IR, MS, elemental analysis, etc., with interpretation) should be provided in support of the structure and stereochemistry.

3.2.S.3.2 Impurities *(name, manufacturer)*

Provide a description of impurities, indicating the possible source of impurities and a clear distinction between actual and possible impurities.
Provide a description of possible degradation products.

3.2.S.4 Control of active pharmaceutical ingredient *(name, manufacturer)*

3.2.S.4.1 Specifications *(name, manufacturer)*

Include the API Manufacturer's and FPP Manufacturer's (if different) specifications of the active pharmaceutical ingredient in tabulated format, not narrative. Indicate clearly if these specifications are the same.

Additional specifications e.g. isomers, chirality, polymorphs, as well as impurities, particle size distribution, residual solvents, where relevant, should be submitted for all APIs.

Specifications and the control procedures for the particle size of APIs which have a low solubility in water in accordance with the BCS definition and for those which the Council may request, should be submitted and the solubility quantified unless justified. Particle size should be stated in SI units (μm). Exemption from this requirement may be granted if the API is administered as a clear solution.

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

Include detailed methods used for quality testing (identification, assay, determination of related substances, residual solvents etc., including chromatograms for the API Manufacturer and FPP Manufacturer (if different). When pharmacopoeial methods are used these should be current and may be referred to.

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

Include validation reports, where relevant. In-house methods require full validation. Pharmacopoeial methods require system suitability and linearity where applicable.

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

For NCEs extensive batch analysis is required, also for batches used in clinical studies.

Submit valid certificates of Analysis (CoAs) from the API manufacturer relating to at least two batches for NCEs and generics.

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

Full justification is required for in-house standards claimed (refer ICH Q6A).
No justification is required for pharmacopoeial standards claimed unless there are additional tests.

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

For NCEs and well-known non-compendial APIs at least the following information on the primary reference standard should be presented:

- Purification method if applicable
- Establishment of purity (potency)
- CoA, with a potency statement

If a pharmacopoeial monograph is claimed, the pharmacopoeial standard should be used.

Secondary standards should always be established against the pharmacopoeial/primary standard.
Refer: WHO Technical Report Series 943, Annex 3 (2007)

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 drawing, 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 e.g. choice of materials, protection from moisture and light, compatibility of the materials of construction with the API, including sorption to container and leaching, and/or safety of materials of construction

3.2.S.7 Stability (name, manufacturer)

3.2.S.7.1 Stability summary and conclusions *(name, manufacturer)*

The storage requirements for the API as specified by the manufacturer of the API and/or prescribed in the pharmacopoeia or acceptable standard reference should be stated and a description of the API container closure system be included. If a specific storage temperature is not specified in any acceptable reference, an instruction to protect from excessive heat, freezing and moisture and light should be included unless justified.

The proposed retest period should be stated.

Note: Only a shelf-life and not a retest period is allocated to an antibiotic of natural origin and for biological APIs and intermediates thereof.

3.2.S.7.2 Post approval stability protocol and stability commitment *(name, manufacturer)*

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

(1) Include results of stability studies performed on the API obtained by the route of synthesis described in Module 3.2.S.2.2when stored in the proposed container closure system.

(2) Provide the conditions under which degradation products are formed (stress testing).

(3) A validated stability-indicating assay method, described in full, should be used in these studies, unless the method for related substances is specific and quantitative (HPLC).

(4) Supporting chromatograms, where relevant, should be included in the methods or validation section.

(5) Stability data on new chemical entity APIs should be generated according to the Stability guideline. For well-known chemical entities supporting literature may be submitted.

(6) For biological medicines stability of the primary production lot and all intermediates (if not used immediately) should be provided.

3.2.P Pharmaceutical Product*(name, dosage form)*

3.2.P.1 Description and Composition of the pharmaceutical product *(name, dosage form)*

(1) The formulation should show the INN or approved names, and/or chemical names of all APIs, and polymorph (if relevant)and approved names of inactive pharmaceutical ingredients (IPIs), including those that do not remain in the final product after manufacturing e.g. granulating agents and gases used for flushing. IPIs not present in the final product should be indicated.

The ingredients for *in-situ* preparations, pre-mixes, FPP intermediates, cores, coating etc, should be listed/grouped together and identified accordingly.

(2) The name and the quantity of the API and the name and quantity stated under "Composition" in the package insert and PIL should correspond. The name and quantity of the API per dosage unit should also correspond to the final product specifications.

Justification should be provided for deviations.

The theoretical quantity of the base of the API should be stated if a compound, e.g. hydrate, solvate, salt is used.

If the moisture content or other characteristic of an API is relevant to the quantity of the IPIs used in the formulation, this should be mentioned in a footnote.

(3) A product may contain more than one API provided that:

a) each API makes a contribution to the claimed indications;

b) the effect of combining the APIs in one product does not decrease the safety, efficacy or quality (including stability)of the product significantly; and

c) the product provides rational concurrent therapy for a significant proportion of the target population, e.g. tuberculostatic combinations.

(4) Each pharmaceutical ingredient should be listed with its quantity per dosage unit. This would include the vehicle(s), solvent(s) or base(s) (excluding quantities of coating solvents). In the absence of an approved name (INN) or chemical name, a chemical description or characterisation of the substance, should be given. If so required and relevant, the proprietary name of the IPI may be included in addition to the approved name.

The approved name for each ingredient should be standardised throughout the application.

Where applicable, special characteristics of the IPI, e.g. lyophilised, micronised, solubilised, emulsified, or form (e.g. anhydrous, monohydrate) and/or source (e.g. the botanical source of starch) should be indicated.

The grade of IPIs, also when a pharmacopoeial monograph covers more than one grade, (e.g. viscosity of methyl cellulose) and the type of water (e.g. purified, WFI), where relevant, should be indicated.

The use of IPIs that are not described in official pharmacopoeiae is strongly discouraged and should be justified. For flavourants, fragrances, colourants and inks refer to (9)

(5) The purpose of each IPI should be stated briefly. If the IPI is used for multiple purposes in the formulation, each purpose should be mentioned.

The name of each API and IPI should correspond and the quantities correlate with those reflected in the batch formulation submitted in Module 3.2.P.3.2 and the batch manufacturing record submitted or made available for inspection.

(6) Some IPIs are single chemical entities while others are combinations. Some are chemically transformed, e.g. modified starch. For excipients that are mixtures of chemically related or unrelated components, e.g. polyol esters (mixture of mono, di and triesters), direct compression excipients, solutions or film coating formulations, or excipients that are chemically modified, the nature and quantity of each such excipient should be specified.

3.2.P.1 Description and Composition of the pharmaceutical product (name, dosage form) continued

The qualitative composition of inks should be specified.

The composition of these mixtures / combinations could be attached to the formulation information / included separately on the following page.

(7) Any overages for the API should be stated separately. The label claim quantity should be stated and the excess quantity indicated as the actual quantity or as a percentage. For example, 500 mg + 5 mg (= 1 %) overage*

(*Use the asterisk to indicate the justification for the overage).

The reason for the overage should be stated / justified, e.g. with reference to batch results, in 3.2.P.2.2.2.

(8) If a potency adjustment for the API has to be made, a statement to the effect that the actual quantity of the active will depend on the potency and the IPI(s) that will be used to adjust the bulk quantity should be made. The manner in which the adjustment will be made should also be specified.

If the moisture content or other characteristic of an IPI is relevant to the quantity of the IPI used in the formulation, this should be mentioned in a footnote.

(9) Permitted flavouring and colouring agents (that comply with The Foodstuffs, Cosmetics and Disinfectants Act, Act 54 of 1972or with directives of the EU or the register of the FDA.), because of their complexity in many instances, may be described in terms of their main constituents only, provided that a conclusive identification is given in the relevant section.

The Colour Index Numbers (Foodstuffs, Cosmetics and Disinfectants Act, 1972 Regulation Food Colourants) or the colourant reference number in accordance with the EU directive of colourants should be included in the formulation.

The use of dyes, printing ink, coating materials, flavourants and organic solvents is subject to the same safety and quality requirements that apply to medicinal substances.

(10) The content of alcohol, if included in medicines for oral administration, should comply with the requirements of the Alcohol Content of Medicines guideline.

(11) If a vehicle is added up to the required volume or mass of the product, the actual or estimated quantity of that vehicle may be stated. Expressions such as “add up to” and “q.s.” are however acceptable. Solutions added to adjust the pH should be described in terms of composition and strength (e.g. normality, molarity), but it is not necessary to state the actual quantity added as none or only minute quantities may be required.

(12) In the case of capsules, the fill mass as well as the capsule size, composition and mass should be indicated.

(13) The theoretical mass must be indicated for uncoated tablets. In the case of coated dosage forms, the theoretical mass of the core, coating material, as well as the total mass of the dosage form/unit should be indicated and the IPIs used for each should be grouped separately.

(14) For biological medicines, the details of any solution supplied by the manufacturer for the reconstitution before use of a dried biological medicine that is offered for sale in a dried form, should be supplied.

(15) Toxicity levels per dosage unit should be indicated for all solvents and for other ingredients when required by Council. Levels should be indicated as per the most recent edition of the Martindale The Complete Drug Reference.

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

A Pharmaceutical Development Report (generally of not more than 25 A4 pages) should be submitted with each application and should include at least an overall conclusion and the following:

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

3.2.P.2.1.1 Active Pharmaceutical Substance(s) *(name, dosage form)*

- Comment on the synthesis of the API(s);
- Discussion on all physico-chemical properties, e.g. solubility (in terms of BCS classification), water content, particle size distribution, crystal properties, polymorphs, chirality, isomers, stability of the API that can influence the performance of the final product should be discussed.
- The compatibility of the API with excipients listed in 3.2.P.1 should be discussed.

  Provide studies (literature) with proposed excipients. If the excipients are the same as those of the reference product, this is not required.
- In case of fixed-dose combination products extensive studies on API-API compatibility under various conditions (aqueous medium and solid state) should be provided. For well-established combinations literature information may suffice, if available. In general, the pharmaceutical development and quality aspects of FDC products should be in accordance with WHO Technical report series 929 “Guidelines for registration of fixed-dose combination medicinal products 2005” or the latest revision.

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

- Submit an explanation of the function of the IPIs.
- For multisource products, state whether excipients are the same as in the reference product.
- Non-compendial IPIs should be avoided in generic products. Submit the safety/toxicity profile of the IPIs if not compendial.

3.2.P.2.2 Final pharmaceutical product *(name, dosage form)*

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

- Data or literature (including the qualitative composition of the innovator product) on any interactions likely to occur, or that may occur, under given circumstances between the API and excipients;
- For multisource products include a tabulated comparison of the qualitative composition, appearance, physical parameters, impurity profiles and other relevant parameters of the test and reference/innovator products;
- Discussion of the relevant physico-chemical parameters e.g. dissolution and choice of medium, effect of pH. The dissolution conditions and acceptance criteria should be derived from the multipoint comparative data generated for the batch used in the BE/biowaiver studies
- Scoring of tablets
  - Functional scoring:

    Provide data of a study on the uniformity of dosage units of the tablet halves in terms of USP or Ph.Eur./BP. This test may then be excluded from FPP specification.

    It should be in line with dosage and directions for use (PI/PIL).
  - Non-functional scoring:

    This should be motivated / justified. It should be indicated as non-functional in PI/PIL.
- Pre-formulation testing
- Clinical trial formulations
- Discussion or explanation of novel formulations and novel IPI composition, function and safety

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

- Any differences in the formulation during the development must be indicated clearly in tabulated form (*cf* Module 1.2.2.3)
- Stability (may refer to Module 3.2.P.8)
- Discussion of the stability of the final product formulation, the parameters and specifications used during stability and to confirm quality for lot release
- Conclusion on stability and shelf-life allocation.

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

- A justification/explanation for overages.
- Overages for the sole purpose of extending the shelf-life of the FPP are generally not acceptable, unless justified.

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

- Parameters relevant to the performance of the final product such as pH, ionic strength, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency, and/or immunological activity, should be addressed.
- Show that no precipitation will occur with poorly soluble APIs formulated at a non-physiological pH or formulated with co-solvents (IM, SC, IV).

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 critical aspects should be explained. Where relevant, the method of sterilisation should be explained and justified, *and* compatibility with production equipment e.g. filter media

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.

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 storage, transportation (shipping) and use of the final 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, injections with rubber closures), safety of materials of construction, and performance (such as reproducibility of the dose delivery from the device when presented as part of the FPP product e.g. inhalers/aerosols).

3.2.P.2.5 Microbiological attributes *(name, dosage form)*

Where appropriate, the microbiological attributes of the dosage form should be discussed, including e.g. the rationale for not performing microbial limit testing for non-sterile products and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. This should be determined on at least one stability batch (ageing).

For sterile products the integrity of the container closure system to prevent microbial contamination should be addressed; in-use stability testing whether there is a preservative or not – including eye drops.

See also 3.2.P.8

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

The compatibility of FPP with

- Reconstitution diluent(s)
- IV solutions – provide data or reference to primary references
- Dosage devices (e.g. precipitation of API in solution, sorption on injection administration sets, adsorption by in-line filters

should be addressed to provide appropriate and supportive information for the labelling.

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

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

If more than one pharmaceutical manufacturing facility/site is involved in any of the manufacturing or packaging processes, the complete name and physical address of each site should be given and the various stages of manufacturing and packaging at each site clearly identified and the declaration of similarity included in Module 1.5.2.3. If the methods are not similar, Module 3.2.P.2.3 should be completed as well. If all the stages of manufacturing and packaging are performed at one site a statement confirming this will suffice.

An inspection flow diagram, also of FPP intermediates, clearly indicating the sites and processes, including clear distinction between primary and secondary packers, should be included. [Module 1.7.12]

3.2.P.3.2 Batch formula *(name, dosage form)*

The batch manufacturing formulation, also for FPP intermediates, and the batch size(s) (number of dosage units) should be included. If more than one batch size is indicated, the batch formulation for each of the batch sizes should be given.

3.2.P.3.3 Description of manufacturing process and process controls*(name, dosage form)*

The following should be submitted:

- A comprehensive flow diagram, detailing the various stages of manufacturing -

and

- A comprehensive description of the manufacturing procedures detailing the various stages of manufacturing – derived from the master manufacturing documents.

  The type and size of manufacturing equipment (including sieve sizes in metric units), duration of treatment, temperature, light and humidity conditions, machine settings (e.g. rotation speed or rpm) and other relevant detail should be indicated.

  For sterile manufacturing the grades of clean areas should also be indicated.

and

- A brief description of the packaging procedure -

  A brief description of the packaging procedure reflecting the stages, temperature, humidity and other conditions applicable for the packaging of specific dosage forms e.g. effervescent tablets and granules should be included.

  For sterile manufacturing the grades of clean areas should also be indicated.

The frequency of all in-process control tests (analytical, microbiological, physical, packaging and labelling) should be shown in the flow diagram or specified in the description.

In addition:

Either a copy of the Master Batch Manufacturing and Packaging Document or Records for a batch or the Batch Records should be available for inspection, or be available on request.

3.2.P.3.4 Controls of critical steps and intermediates *(name, dosage form)*

The frequency of all in-process control tests (analytical, microbiological, physical, packaging and labelling) should be shown in the flow diagram or specified in the description.

3.2.P.3.5 Process validation and/or evaluation *(name, dosage form)*

A process validation protocol (VP) or report (VR) should be submitted (refer to the SA Guide to GMP).

The validation of the maximum holding time of the final product before packaging and the holding time of FPP intermediates before further processing should also be addressed. The conditions during storage and/or shipping should be covered.

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

If different sterilisation methods are used, validation of each method should be addressed in the validation protocol or report provided. This would include a description of the sterilisation processes, aseptic manipulation, in-process controls, grades of clean areas. Validation should include the validation of the maximum holding time before packing into the final container and the holding time of FPP intermediates before further processing.

New Applications for registration:

A VP or a VR should be included in3.2.P.3.5. If the VP is submitted the VR should be submitted only if and when requested by the Regulatory Authority.

Applications for change in applicant/manufacturer/packer/laboratory:

A VP or VR should be submitted with each application for a change in manufacturer or laboratory, or change in applicant where it also involves a change in manufacturer.

If the validation has already been done, it should be indicated as such in the application and the VP and VR have to be submitted.

3.2.P.4 Control of Inactive Pharmaceutical Ingredients*(name, dosage form)*

The approved name of each ingredient should concur with that reflected in the formulation in 3.2.P.1.

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

Compendial and Non-compendial

(1) Specifications (titles and the limits) of all the inactive pharmaceutical ingredients, also the IPIs of FPP intermediates, should be listed. Adherence to current pharmacopoeial requirements (BP, USP and Ph.Eur.), where applicable, is recommended, in which case it is not necessary to list specifications. Any deviation from such specifications should be fully substantiated, e.g. non-inclusion of a specific impurity specification due to a different route of synthesis.

Use of any other pharmacopoeia should be justified and acceptable to the Council. In the latter case, copies of the relevant monographs should be included.

More than one pharmacopoeia may be used for the inactive pharmaceutical ingredients, provided that each individual reference is used fully, and not partially or selectively. For example,

- the USP may be used for starch and the BP for lactose;
- an individual IPI may be referenced fully to two or more recognised pharmacopoeiae simultaneously;
- an in-house specification consisting of all parameters and which includes the most stringent criteria of acceptance of two or more recognised pharmacopoeiae.

For non-pharmacopoeial entities the specifications should be at pharmacopoeial level, i.e. based on current pharmacopoeial requirements for similar pharmacopoeial entities. (See ICH Q6A)

(2) Functionality specifications which confirm the IPI characteristics should be indicated.

(3) Colourants and flavourants should comply with either one of the following:

a) At least a specification and control procedure regarding the chemical identification, and a statement that the flavourants comply with the general requirements and that the colourants comply with the purity criteria of The Foodstuffs, Cosmetics and Disinfectants Act, Act 54 of 1972.

b) At least a specification and control procedure regarding chemical identification and a statement that it complies with the directives of the EU or the register of the FDA.

3.2.P.4 Control of Inactive Pharmaceutical Ingredients (name, dosage form) - continued

(4) Microbial limits and control procedures for all organic ingredients of natural origin, should be included *[(e.g. maize starch is an organic IPI of natural origin (test), but selenium dioxide is an inorganic IPI of natural origin (no test)].*

(5) Empty capsule specifications should include the description, moisture content, disintegration time and microbial limits.

(6) The absence of diethylene glycol should be specified for propylene glycol and glycerine if the dosage form is for oral or parenteral administration.

(7) Specifications and control procedures should be included for intermediate preparations used as ingredients in the formulation as well as for each of the ingredients contained in the intermediate preparation. If stock preparations of the intermediate preparation are used, specification and control procedures to ensure the stability and confirm the identity should be included.

(8) For biological medicines:

a) Specifications for the primary production lot used in the manufacture of the final filling lot of a biological medicine and specifications for all ingredients for the diluent should be listed.

b) Tests for a biological source material should include tests to confirm the identification, safety and potency of the primary production or bulk lot used in the manufacture of the final filling lot.

c) Parameters and criteria of acceptance to confirm the identification, safety and potency of the product should be provided.

3.2.P.4.2 Analytical procedures *(name, dosage form)*

Control procedures for all inactive pharmaceutical ingredients should be fully described. These should include physico-chemical tests, purity tests, solubility and assay and any other relevant tests. When pharmacopoeial methods are used these should be current and may be referred to.

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. (Refer ICH Guidelines Q2R1, Q6B)

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

Justification for the proposed excipient specification should be provided, where appropriate. (Refer ICH Guidelines Q3C and Q6B)

3.2.P.4.5 Excipients of human or animal origin *(name, dosage form)*

Refer to 3.2.R.6 and ICHM4Q

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

For excipients(s) used for the first time in a FPP or by new route of administration, full details of manufacture, characterisation and controls, with cross-references to supporting safety data (non-clinical and/or clinical) should be provided according to the API format. (Details in 3.2.A.3)

3.2.P.5 Control of pharmaceutical product *(name, dosage form)*

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

Specifications

(1) Specifications (titles and limits) should be listed for in-process controls, FPP intermediate controls, final product controls (batch release), stability controls and the reconstituted or diluted final product (if applicable). [If the in-process controls are submitted in3.2.P.3.3a cross reference will suffice. In-process controls should be clearly identified as such including those performed on bulk e.g. liquids and semi-solids prior to packaging.]

If a product is included in a recognised pharmacopoeia any deviation from the relevant monograph should be justified.

(2) The description of the final product and the description given under “Identification” in the package insert should correspond. The description should be such that visual identification of counterfeit medicines is facilitated where possible.

(3) See Appendix 2 of the Stability guideline for the minimum suggested specifications required for each dosage form. If any specification is not appropriate for a particular product, a motivation should be included. Other parameters not appropriate for stability testing should also be included, e.g. a specification for residual organic solvents used during the coating procedure, or sterility.

The limits and acceptance criteria for each parameter (physical, chemical and if applicable microbial) should be fully described, to state "complies" for acceptance criteria is not acceptable.

Physical and other properties

(4) At least the following physical and other properties additional to those listed in the Stability Guideline, should be specified as appropriate for the dosage form, unless the omission is justified:

a) Tablets, lozenges, capsules, suppositories

Theoretical mass, average mass and mass limits, uniformity of dosage units, divisibility of scored tablet with the relevant mass uniformity of the divided tablet

Intactness of coating in the case of coated tablets if the coating has a protective purpose; if not appropriate for a particular product (e.g. film coat) a motivation should be included.

Microbial testing as lot release requirement for capsules is not a requirement if microbial testing of the empty capsules is performed and submitted in 3.2.P.4

For soft gelatin capsules containing oily liquid, peroxide value / acid value / iodine value/ and any other appropriate parameter, suspension content uniformity of each active.

b) Emulsions, suspensions, solutions

Alcohol content, tonicity (eye and nasal preparations), fill volume or mass, deliverable volume. Peroxide value / acid value / iodine value/ and any other appropriate parameter for oily preparations.

c) Powders, granules (including those for reconstitution), metered dose inhalation aerosols

Fill volume or mass

d) Ointments, creams

Peroxide value / acid value / iodine value / and any other appropriate parameter for oily preparations

e) Parenterals

Evaluation of FPP intermediates for parenterals should also include homogeneity, and FPP intermediate sterile powders should also include evaluation of sterility and bacterial endotoxin testing (BET).

f) FPP Intermediate (defined in SAGMP – partially completed final product, pre-mixes, microspheres, granules, coated granules, sterile powders etc.)

FPP Intermediates should also include evaluation of homogeneity and other appropriate parameters relevant to the FPP intermediate product/dosage form.

Assay / content

(5) The limits of acceptance for the content of each active ingredient should be expressed as a percentage of the label claim. Limits greater than 5,0 % of the label claim should be justified if not vitamins.

(6) Uniformity of dosage units should be in accordance with the general requirements of the current editions of the official pharmacopoeiae. Note that the uniformity has been harmonized in the ICH region (see ICH guideline Q4B Annex 6).

Also refer to the WHO Technical Report Series 929 "Guideline for the registration of fixed-dose combination medicinal products 2005" or the latest revision.

FPP intermediates, including parenterals, should also be evaluated for homogeneity - *refer (4) above.*

Dissolution and disintegration

(7) Batch release and stability specifications for all solid oral dosage forms, including chewable tablets, and suspensions where applicable, should include a requirement for the dissolution of the active pharmaceutical ingredient(s), (generally single point for immediate release, multipoint for modified release) unless otherwise determined by Council.

(8) Disintegration time, where relevant, for example for chew tablets, matrix tablets and soft gelatin capsules, should be determined on all batches on which dissolution is not determined as a requirement for lot release as well as for stability. Disintegration time may be used as a lot release requirement for preparations containing multivitamins and minerals, unless a dissolution requirement for a specific product is included in the USP, in which case dissolution should be done as a lot release requirement.

Preservative efficacy

(9) The preservative efficacy of relevant dosage forms and/or presentations, e.g. multi-dose vials, eye drops should be specified in 3.2.P.5.1and presented in 3.2.P.8. However, once established for the lowest limit of preservative content specification, it is not a routine batch test requirement.

Endotoxins

(10) For a product from a non-biological origin which has endotoxin levels, the validation data as required by the USP / BP/ Ph.Eur., should be submitted.

(11) If the endotoxin levels are not determined according to the method in a recognised pharmacopoeia, the validation data should be submitted for evaluation.

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

All control procedures, other than those from a recognised pharmacopoeia, should be described in full and calculations included where relevant.

If an analysis is not technologically possible, e.g. complex extracts, a motivation and alternative quality criteria should be submitted.

3.2.P.5.3 Validation of analytical procedures *(name, dosage form)*

(1) The full validation data of the assay method of the API related to batch release should be submitted. Chromatograms confirming the separation of the API from the degradation products, if relevant, should be included.

(2) It should be demonstrated that the assay method is stability-indicating, i.e. it should distinguish between the API(s) and the degradation product(s).

(3) If the assay method used to determine the API content is not stability indicating, it cannot be used for assaying after importation.

(4) If the assay method (chromatographic) is taken from one of the latest recognised pharmacopoeias other partial validation data, e.g. system suitability and specificity, should be submitted.

(5) If an assay method different from the batch release method is used for stability testing, the validation of the assay method and a full description thereof, should be submitted.

(6) Supportive chromatograms, if relevant, for the validation should be submitted.

(7) All other quantitative assay methods (e.g. preservatives, degradation products, antioxidants, dissolution assay) should be validated and the validation data included.

If not in accordance with the relevant pharmacopoeia, a motivation should be included for the deviation.

The content of each preservative and anti-oxidant should further correlate with those stated in modules 1.3 and 3.2.P.1. All the relevant limits should also be justified by stability or batch data.

3.2.P.5.4 Batch analyses *(name, dosage form)*

(1) Complete batch analysis data for at least two batches (pilot or production) of the final product should be submitted with the application.

(2) For imported products at least the identification and assay of the API content should be performed by an approved laboratory (FPRC) after importation. This is to verify that the product has not been affected adversely during transportation. [File under Module 1.7.4] Exemption from this requirement may be applied for according to the Post-Importation Testing of Medicines guideline.

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" (Refer ICH Guidelines Q3B, Q5C, Q6A, Q6B)

3.2.P.5.6 Justification of specifications *(name, dosage form)*

Justification for the proposed final product specifications should be provided. (Refer ICH Guidelines Q3B, Q6A and Q6B).

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

For NCEs and well-known non-compendial APIs at least the following information on the primary reference standard should be presented:

- Purification method if applicable
- Establishment of purity (potency)
- CoA, with a potency statement

If a pharmacopoeial monograph is claimed, the pharmacopoeial standard should be used.

Secondary standards should always be established against the pharmacopoeial/primary standard. *Refer WHO Technical Report Series 943, Annex 3 (2007)*

3.2.P.7 Container closure system *(name, dosage form)*

(1) The immediate container specifications (titles and limits), including the nature of the material, dimensions and sketches where applicable, as well as those of patient ready packs, the closure system, wadding and any other component in direct contact with the product, where applicable, and a description of the control procedures, should be supplied.

These should include the

- moisture and gas permeability of PVC, if not already supported by real time stability data of the product (not relevant for PVC forming a base layer of aluminium blisters) and
- heat seal bond strength / intactness of the blister (integrity of the seal) – 3.2.P.3.3 may be referred to.

(2) A description of the control procedures performed by the manufacturer of the final product should be given.

(3) A brief description of the outer container, if any, should also be given. At least the nature of the material should be mentioned, e.g. outer cardboard carton.

(4) The description of the container and that reflected in the package insert under "Presentation" and in the stability studies should correspond. To facilitate the visual identification of counterfeit medicines (also by the public) the description should include the type, colour, and clarity of the container, e.g. white opaque securitainer, clear plastic/silver aluminium blister.

(5) If the product is packed in bulk containers, the type of material of the container, should be stated.

The maximum period that the product may be stored (bulk) before final packaging should be given in Module 3.2.P.3.3, the nature of the container should be given in Module 3.2.P.7 and supporting data provided in Module 3.2.P.8.

(6) The type of material and the dimensions, including sketches of ampoules, vials, aerosols, applicators and administration sets should be given. Sketches of containers for oral dosage forms and blister packs are not required.

(7) All pack sizes should be described in the submission.

(8) If equivalent or more protective immediate container packaging material than used in stability testing or approved (post-registration),is applied for, data to substantiate the claim should be submitted, e.g. USP permeation test.

(9) Child-protective measures must be employed with regard to the retail sale of salicylates, paracetamol and iron tablets or capsules.

Smaller sales packs and blister packaging are regarded as suitable child protective measures.

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

3.2.P.8.1 Stability summary and conclusion *(name, dosage form)*

A tabulated summary of the data, clearly indicating the number and types / sizes (production, pilot or experimental) of batches, packaging material, storage conditions and storage period, and manufacturer of the API with API batch numbers, should be included for each final product manufacturer.

3.2.P.8.2 Post-approval stability protocol and stability commitment *(name, dosage form)*

3.2.P.8.3 Stability data *(name, dosage form)*

All applications for registration of a medicine should be submitted with stability data in accordance with the minimum requirements stated in the Stability guideline.

3.2.A APPENDICES

3.2.A.1 Facilities and equipment *(name, manufacturer)*

3.2.A.2 Adventitious agents safety evaluation *(name, dosage form, manufacturer)*

3.2.A.3 Excipients

3.2.R REGIONAL INFORMATION

3.2.R.1 Pharmaceutical and Biological availability

I 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 Biostudies 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 Biostudy guideline as well as the Dissolution guideline.

b) *In vitro* dissolution

The studies should be carried out in accordance with the Dissolution guideline.

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.

3.2.R.1 Pharmaceutical and biological availability - continued

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.

II 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 MCC.

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.

II STUDY PRODUCTS - continued

(2) Reference Products (comparators)*(see also Biostudies and Dissolution Guidelines)*

N.B. Products containing chemical entities/active moieties that are not registered in South Africa cannot be used as reference products in efficacy and safety studies submitted in support of an application.

Copies of the labelling (label(s) and package insert) for the reference as well as the innovator product marketed in South Africa should be provided in3.2.R.1.2except as under point a)(iii) below, in which case an MCC approved package insert for a generic or similar product should be submitted if available.

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 Council may be acceptable.

Product strengths not available in South Africa may be applied for and/or used in biostudies provided that the dose range is approved/registered in South Africa.

a) Selection of Reference Product

The reference product should be an innovator product registered by Council and should be preferably procured in South Africa. 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 South African market. 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 South Africa; or

(ii) the innovator product, registered in South Africa, for which a marketing authorization has been granted by the health authority of a country with which Council aligns itself (see General Information guideline 3.1.4), 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 *(see also Biostudies and Dissolution Guidelines)*

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 MCC 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.R.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.3.5respectively.

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.3.5respectively.

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.

3.2.R.1.1 Overview - continued

Proof of physico-chemical equivalence is required if the manufacturer of the API is additional or different to that stated in 3.2.Sand 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.3.5respectively.

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 choice of reference product should be justified by the applicant.

Reference products registered in South Africa but procured in another country, the health regulatory authority of which the MCC aligns itself with ("foreign" reference product).

The following additional information should be supplied when the Biostudy reference product used is registered but not procured in South Africa:

1) The name and address of the manufacturing site where the reference product is manufactured.
2) The qualitative formulation of the reference product.
3) Copies of the immediate container label as well as the carton or outer container label of the reference product.
4) For modified release, evidence of the mechanism of modified release of the reference product.
5) The method of manufacture of the reference product if claimed by the applicant to be the same.
6) 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*

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 South Africa, the labelling / SPC / Package insert of the reference product translated into English if not in English, as well as the package insert of the relevant innovator product in South Africa.
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 (Biostudies guideline 3.9.1 h)
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 to include the innovator product in South Africa or other information*
- *e.g. if the biostudy reference product is not the innovator registered and on the market in South Africa an extra column for the details of the innovator product in South Africa corresponding to that of the biostudy reference product is appropriate. Extra rows may be included as required to reflect e.g. more detailed dissolution results or similarity factor values, or page numbers of documents.*

Product Information	**Reference Product(s) of Biostudies**	**Corresponding RSA Reference product**	**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*	*if known/relevant*	**
Batch size	*if known/relevant*	*if known/relevant*	
Product status	Clinical trial formulation *or* Innovator product *or* Current formulation (for change of formulation) *as the case may be*	Clinical trial formulation *or* Innovator product *or* Current formulation (for change of formulation) *as the case may be*	
CoAs, test and reference products and API of test product study batch	3.2.R.1.3 p	3.2.R.1.3 p	3.2.R.1.3 p
Package insert	3.2.R.1.2 p	3.2.R.1.2 p	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 Overview - continued

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)

1) Package inserts
2) label and carton,
3) qualitative formulation,
4) proof of procurement/invoice(foreign product)

3.2.R.1.3 Certificates of Analysis

1) Biostudy reference product
2) RSA corresponding innovator
3) Biostudy test product and any other strength
4) API of the test product
5) 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
2) Comparative dissolution between foreign reference product and RSA registered innovator product (if applicable)
3) Comparative dissolution between different strengths of the test product (biowaiver of additional strengths)
4) Comparative dissolution between test and reference products (BCS biowaiver)
5) 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 Biostudies guideline section 4), and comparison of final product characteristics.

3.2.R.2 Parent API manufacturer with various sites

1) 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.
2) 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) Confirmation of WHO API Prequalification (CPQ)

1) 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 the CEP is accompanied by any annexes mentioned in 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)

2) A valid Confirmation of Active Pharmaceutical Ingredient (API) Prequalification document (CPQ) may be submitted for an API if available.

The CPQ is a confirmation document provided by the WHO prequalification (PQ) of Medicines Programme/Team indicating that the relevant API has been evaluated and conforms to the WHO requirements for prequalification of APIs. The CPQ document contains the accepted retest period and storage conditions, the accepted API specifications and copies of the assay and related substances test methodology. The CPQ document may be provided by the API manufacturers to interested parties at their discretion.

The prequalification status of the API and associated details can be verified from the WHO List of Prequalified API web page:

http://www.who.int/prequal/info_applicants/API_PQ-List.htm. Information on CPQs may be obtained on the following link: http://apps.who.int/prequal/info_applicants/API_confirmation.htm

3.2.R.3 Certificate(s) of suitability with respect the Ph.Eur. (CEPs) Confirmation of WHO API Prequalification (CPQ) - continued

a) When submitting a CPQ, please ensure that it is complete and accompanied by the accepted specifications, assay and related substance methodology, retest period and storage conditions. Also ensure that the authorisation box of the CPQ is filled out by the API manufacturer in the name of the manufacturer or applicant seeking to use the document.

b) It is the responsibility of the applicant to be aware of changes in the status of CPQs that are used for their products and to notify Council accordingly. It is also the responsibility of the applicant to ensure that the revised CPQ is obtained from the CPQ holder when applicable and to submit such updated CPQ's. If the CPQ is withdrawn or suspended for whatever reason a DMF or APIF should be submitted within six months, in accordance with 3.2.S.

c) If a CPQ is submitted, detailed descriptions of the methods of synthesis and analysis of the API are not required. The following additional information will be required when not included in the CPQ:

- *3.2.S.1.3 General properties* – discussions on any additional applicable physicochemical and other relevant API properties that are not controlled by the API manufacturer's specifications, e.g. solubilities and polymorphs according to the guidance in this section.
- *3.2.S.2 Manufacture* – if the sterility of the FPP is based upon the sterile manufacture of the API then data on the sterilization process together with full validation data should be provided if applicable
- *3.2.S.3.1 Elucidation of structure and other characteristics* – studies to identify polymorphs and particle size distribution, where applicable, according to the section in this guidance.
- *3.2.S.4.1 Specification* – the specifications of the FPP manufacturer including all tests and limits of the API manufacturer's specifications according to the CPQ and any additional tests and acceptance criteria that are not controlled by the API manufacturer's specifications such as polymorphs and/or particle size distribution.
- *3.2.S.4.2/3.2.S.4.3 Analytical procedures and validation* – any methods used by the FPP manufacturer in addition to those in the API manufacturer's specifications.
- *3.2.S.4.4 Batch analysis* – results from two batches of at least pilot scale, demonstrating compliance with the FPP manufacturer's API specifications.
- *3*.2.S.5 *Reference standards or materials* – information on the FPP manufacturer's reference standards.
- *3.2.S.7 Stability* – data to support the retest period if either the proposed retest period is longer or the proposed storage conditions are at a higher temperature and/or humidity to that of the prequalified API.

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 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:

3.2.R.4.2 Comparative results - continued

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 (1.2.3 a)) 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 Batch records of samples

The batch records of samples must be available for inspection or on request.

3.2.R.8 Other

3.3 Literature references

4 MODULE 5*(for ease of reference, the numbering of module 5 is used)*

Refer also to Biostudies guideline

5.3.1 Reports of biopharmaceutic 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 BA and Bioequivalence (BE) Study Reports *Refer* Biostudies guideline

5.3.1.3 *In vitro-in vivo* correlation study reports

5.3.1.4 Reports of bioanalytical and analytical methods for human studies *Refer* Biostudies guideline

GRANULARITY

The granularity for section 3.2.R

3.2.R	3.2.R.1	3.2.R.1.1	
		3.2.R.1.2	
		3.2.R.1.3	
		3.2.R.1.4	3.2.R.1.4.1
			3.2.R.1.4.2
	3.2.R.2		
	3.2.R.3		
	3.2.R.4	3.2.R.4.1	
		3.2.R.4.2	
		3.2.R.4.3	
		3.2.R.4.4	
	3.2.R.5		
	3.2.R.6		
	3.2.R.7		
	3.2.R.8		

Documents rolled up to this level are not considered appropriate
One document may be submitted at this level

REFERENCES

1) ICH Guidelines (Q1A, Q1B and Q1F 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)
2) WHO Guidelines on Biologicals
3) CPMP Note for Guidance on Development Pharmaceutics (CPMP/QWP/155/96)
4) WHO Technical Report Series 937, 2006
5) WHO Technical Report Series 929, 2005
6) NTA 2B , CTD-Module 3, edition July 2004
7) SA Guide to GMP current version

LIST OF ACRONYMS

API	Active Pharmaceutical Ingredient	FPRR	Finished Product Release Responsibility
APIF	Active Pharmaceutical Ingredient File	FPP	Finished Pharmaceutical Product
BP	British Pharmacopoeia	GMP	Good Manufacturing Practices
BSE	Bovine Spongiform Encephalitis	ICH	International Conference on Harmonisation
CEP	European Certificate of Suitability	INN	International Non-proprietary Name
	(Certificate Europeans Propriate)	IPI	Inactive Pharmaceutical Ingredient
CoA	Certificate of Analysis	MCC	Medicines Control Council
CPQ	Confirmation of WHO API prequalification	NCE	New Chemical Entity
CTD	Common Technical Document	Ph.Eur.	European Pharmacopoeia
cGMP	Current Good Manufacturing Practices	TSE	Transmissible Spongiform Encephalopathy
CV	Curriculum Vitae	USP	United States Pharmacopoeia
DMF	Drug Master File	USP DI	United States Pharmacopoeia Drug Index
EU	European Union	VP	Validation Protocol
EMEA	European Medicines Agency	VR	Validation Report
FDA	Food and Drug Administration (USA)	WHO	World Health Organisation
FPRC	Final Product Release Control		

TERMINOLOGY

Active pharmaceutical ingredient

A substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a therapeutically active ingredient.

Final product

A product that has undergone all stages of production, excluding packaging.

Finished pharmaceutical product (FPP)

A product that has undergone all stages of production, 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.

Manufacture (manufacturing)

All operations of purchase of materials and products, production and packaging, quality control, release, storage, shipment of FPP and related controls.

Medicine

As defined in section 1 of the Act.

Medicinal product

See pharmaceutical product.

Modified-release dosage forms

A modified-release dosage form is one for which the API release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms.

Delayed-release and extended-release dosage forms are two types of modified-release dosage forms.

Delayed-release dosage forms - A delayed-release dosage form is one that releases an API(s) at a time other than promptly after administration.

Extended-release dosage forms - An extended-release dosage form is one that allows at least a twofold reduction in dosing frequency or significant increase in patient compliance or therapeutic performance as compared to that presented as a conventional dosage form (e.g. as a solution or a prompt API-releasing, conventional solid dosage form).

The terms controlled *release, prolonged action,* and *sustained release* are used synonymously with extended release. This document uses the term *extended release* to describe a formulation that does not release an API immediately after oral dosing and that also allows a reduction in dosage frequency. This nomenclature accords generally with the USP definition of extended release but does not specify an impact on dosing frequency. The terms *controlled release* and *extended release* are considered interchangeable in this guidance.

Terminology - continued

NCE

New chemical entity

Pharmaceutical Product

Any preparation for human or veterinary use containing one or more active pharmaceutical ingredients, with or without pharmaceutical excipients or additives, which is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

UPDATE HISTORY

Date	Reason for update	Version & publication
June 2010	First publication released for implementation and comment	Version 1,June 2010
30 September 2010	Deadline for comment	
March 2011	Clarification of policy regarding blended powders; Amendment of the following sections: Introduction 3.2.S, 3.2.S.1.2, 3.2.S.1.3 3.2.S.2.1, 3.2.S.2.2, 3.2.S.2.4, 3.2.S.2.5, 3.2.S.2.6 3.2.S.3.1 3.2.S.4.1, 3.2.S.4.2, 3.2.S.4.3, 3.2.S.4.4, 3.2.S.4.5 3.2.S.5, 3.2.S.6 3.2.P.1 (1), (2), (7), (8), (9), (15), deleted (16) 3.2.P.2.1.1, 3.2.P.2.1.2 3.2.P.2.2.1, 3.2.P.2.2.2, 3.2.P.2.2.3 3.2.P.2.3, 3.2.P.2.4, 3.2.P.2.5, 3.2.P.2.6 3.2.P.3.1, 3.2.P.3.2, 3.2.P.3.3, 3.2.P.3.5 3.2.P.4.1 (1), (2) 3.2.P.4.2 (1), (2), (3), deleted (4) 3.2.P.4.3, 3.2.P.4.4, 3.2.P.4.5, 3.2.P.4.6 3.2.P.5.1 (1), (4) e) & added f), (5), (6), deleted (12) 3.2.P.5.4, 3.2.P.5.5, 3.2.P.5.6 3.2.P.6, 3.2.P.7 (1), (2), (5), (8) 3.2.P.8.1 3.2.R.1 *I, II* (2) 3.2.R.1.1, 3.2.R.1.1.3 5), 3.2.R.1.1.6, 3.2.R.1.1.7, 3.2.R.1.1.8, R 2.R.1.1.9, 3.2.R.1.1.10, 3.2.R.1.1.11, 3.2.R.1.1.12 3.2.R.1.2 4), 3.2.R 1.3 5) Deleted 3.2.R.1.2.17 & 18, deleted 3.2.R.1.3.1.5 3.2.R.1.4.1 5) 3.2.R.1.4.2 2); 3.2.R.2, 3.2.R.3, 3.2.R.4, 3.2.R.4.2, 3.2.R.4.2, 3.2.R.4.4 3.2.R.6, 3.2.R.7 5.3.1, 5.3.1.2, 5.3.1.4 Granularity; replacement of ‘drug’ with ‘API’ in “Terminology” List of Acronyms IFD moved to Guidance for CTD/eCTD General & Module 1	Version 2, March 2011
March 2011	Date of implementation	
June 2011	2.3 QOS 3.2.S.4.1 Specifications 3.2.P.2.2.1, 3.2.P.3.4 , 3.2.P.4.5 3.2.R.1 Pharmaceutical and Biological availability, I SCOPE, 3.2.R.1.1.3, 3.2.R.1.1.6, 3.2.R.1.1.7, 3.2.R.1.1.8 5.3.1	Version 3, June 2011

Date	Reason for update	Version & publication
July 2012	Correction in 3.2.P.3.1 and 3.2.P.4.5	Version 3_1, July 2012
With immediate effect	Date of implementation	
Aug 2014	Correction in 3.2.S.7.1 to include statement re shelf-life of an antibiotic, omitted in error	Version 4, Aug 2014
	3.2.R.3 Addition of WHO API prequalification	
With immediate effect	Date of implementation	