SAHPRA
South African
Health Products
Regulatory Authority

SAHPRA Head Office
Building A
Loftus Park
2nd Floor
402 Kirkness Road
Arcadia
0083

COMPLEMENTARY MEDICINES
REGISTRATION APPLICATION ZA-CTD - QUALITY

This guideline is intended to provide recommendations to applicants wishing to submit applications for the registration of Complementary Medicines. It represents the South African Health Product Regulatory Authority's current thinking on the quality, safety, and efficacy of these medicines. It is not intended as an exclusive approach. The SAHPRA 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 SAHPRA is committed to ensure that all registered medicines will be of the required quality, safety and efficacy. It is important that applicants also adhere to the administrative requirements to avoid delays in the processing and evaluation of applications. Guidelines and application forms are available from the website: www.sahpra.org.za.

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BOITUMELO SEMETE-MAKOKOTLELA

CHIEF EXECUTIVE OFFICER

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Guide for Module 3 Quality:
Chemical, Pharmaceutical and Biological Information for Complementary Medicines, including the subset Health Supplements

1 INTRODUCTION

This document aims to provide guidance on the Quality/pharmaceutical and analytical aspects of the application for registration of a complementary medicine in the Common Technical Document (CTD) format.

It should be read together with the current versions of the following documents, including those referred to therein:

- 6.18 Screening Template for new applications for registration of a Complementary Medicine
- 7.01 Complementary Medicines - Discipline-Specific: Safety and Efficacy
- 7.02 Complementary Medicines - Roadmap and Transitional Process
- 7.03 Complementary Medicines - Use of the ZA CTD format in the preparation of a registration application
- 7.05 Complementary Medicines – Complementary Medicines: Quality
- 7.06 Complementary Medicines - Guidance on Specified Substances

Other SAHPRA guidelines may be referred to where appropriate. A copiy of the referenced guideline should also be supplied.

2 SCOPE

This guideline applies to the quality aspects of an application for registration of complementary medicines submitted in ZA-CTD format. Whilst the completed dossier should be checked for completeness, relevance and correctness, for ease of reference, relevant sections (not a complete list) of Module 1 and Module 2 with which information should be congruent/ should correspond, are indicated.

The requirements for the presentation, labelling, copies and relevant procedures for submission of applications, are stipulated in the General and Module 1 guidance.

The Technical Screening form should be completed to assist with checking of the contents before copying and submission.

2.1 ZA Module 1: Administrative information

Refer to the General and Module 1 guidance.
The information under the following headings in particular should correspond with the information in Module 3.

Module	Heading	Comments/Notes
1.1	Comprehensive Table of Contents (ToC) Modules 1 to 5	Ensure that the volume numbers indicated in the Table of Contents (ToC) correlate with the volume numbers of the final submission copies. Refer to the General and Module 1 guidance for 'Comprehensive Table of Contents' and 'Volume identification'
1.2.1	Application form	Ensure that the relevant product and other details correspond with that in Module 3, e.g. the dosage form, active ingredient(s), strength, route of administration,

Module	Heading	Comments/Notes
		manufacturer, packer
1.2.2.3	Dossier product batch information	Ensure that the batch information corresponds with that in the relevant sections of Module 3 e.g. 3.2.P.5 and 3.2.P.8 and also 3.2.R.1
1.3.1	South African Package Insert	
1.3.1.1	Package insert	Ensure that the proprietary name, dosage form, active ingredient(s), strength, composition, dosage regimen, identification, presentation and storage correspond with the information in Module 3 Ensure that sweeteners are indicated on the label and colourants are congruent with the identification and formulation.
1.3.2	Patient Information Leaflet	
1.3.3	Labels	

2.2 Module 2: Common Technical Document summaries

Module	Heading	Comments/Notes
2.1	**CTD Table of Contents (ToC) Modules 2 to 5**	Ensure that the volume numbers indicated in the Table of Contents (ToC) correlate with the volume numbers of the final submission copies.
2.2	**Introduction**	Describe the product being applied for, include the proprietary name, non-proprietary name or common name of the active substance, the company name, dosage form(s), strength(s), route of administration, pharmacological class and proposed indication(s).
2.3	**Quality Overall Summary (QOS)**	A description of the desired product and product-related substances and a summary of general properties, characteristics, features and characterization data, as described in S.3.1, should be included. The QOS should summarise the data on potential contamination by micro-organisms, products of micro-organisms, pesticides, toxic metals, fumigants, etc. In some specific circumstances, the risk of radioactive contamination is to be considered
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 Module 3 – Quality

Except for the following headings, all the headings of the **ZA CTD Module 3** should be completed as relevant and appropriate for the medicine.

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.5	Medical device
3.2.R.8	Other

3 MODULE 3 – QUALITY REQUIREMENTS

(i) General

This guideline is a best practice guide, indicating the exact location of the relevant parts of the information required in the Module 3 sections, i.e. the "Body of Data" of the ZA CTD.
The principles of GMP are applicable.
It is the applicant's responsibility to ensure that all relevant legislation and guidelines are taken into account in the preparation of each Module and section of the dossier.
This Module of the Application for the registration of a medicine, concerns demonstration of the quality of the product, including the identity, impurities and stability of the ingredients. The data assessment also takes into account the manufacturing processes and standards of good manufacturing practice (GMP), as required.
Details of quality control measures are required to demonstrate that the product will be produced to a consistent quality. Stability data for the product are required to determine a shelf life during which the product's quality is maintained. Should the results of any testing be outside the acceptable limits then appropriate action, which may include rejection or destruction, must be taken immediately**.**

(ii) Compliance with environmental and other requirements

With regard to origin or source of ingredients/materials unless from a licensed cultivated, legal source, no animal or plant source should be included that are included in the lists of the following:

- IUCN Red Data List, (http://www.iucnredlist.org/technical-documents/categories-and-criteria) or
- South African National Biodiversity Red List of South African Plants (http://redlist.sanbi.org/redcat.php) as Near Threatened (NT), Vulnerable (V), Endangered (EN), Critically Endangered (CE) or Extinct in the Wild (EW),

The principles of the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) of which South Africa is a member, must be adhered to.
Applicants may require a Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) import permit if making use of substances (e.g. Hoodia, etc) listed under the National Environmental Management: Biodiversity Act, 2004 (Act 10 of 2004).
Any complementary medicine that is of animal origin must comply with the requirements of the Animal Diseases Act, 1984 (Act 35 of 1984). Any complementary medicine which contains any genetically modified ingredients must comply with the provisions of the Consumer Protection Act, 2008 (Act 68 of 2008).

(iii) Accepted pharmacopoeiae and other standard references

The following pharmacopoeiae and international standards are currently considered acceptable in their entirety:

- United States Pharmacopeia (USP) including Dietary Supplements Compendium
- British Pharmacopoeia (BP)
- European Pharmacopoeia (Ph. Eur.)
- Pharmacopée française (Ph.f.)
- Pharmacopoeia Internationalis (Ph.I.)
- Japanese Pharmacopoeia (JP)
- Food Chemicals Codex (FCC)
- Deutsches Arzneibuch (DAB)
- Deutsches Homöopathisches Arzneibuch (HAB)

Applicants may choose to follow pharmacopoeiae or references of equivalent standard other than those identified that may be more appropriate for specific ingredients or products.

Other pharmacopoeiae or monographs may be used with suitable motivation of its/their equivalence in standing and quality to any of those listed above.

The SAHPRA accepts the use of alternate methods that meet pharmacopoeial requirements. When alternate methods are used for testing to meet pharmacopoeial specifications, the relevant pharmacopoeia should be consulted for information on whether or not the alternate methods are considered suitable.

It is expected that if a monograph is published in one of these pharmacopoeiae, the pharmacopoeial monograph specifications should be considered as minimum specifications used for testing of the medicinal ingredient and finished product. If the product specifications do not include tests and tolerance limits as per the pharmacopoeial monograph, there should be justification as to why the testing is not necessary. The current official version of the pharmacopoeia should be used in all cases. In order to comply with pharmacopoeial monographs, the monograph in its entirety should be applied, including all other pharmacopoeial requirements. It is not acceptable to apply requirements from different pharmacopoeial monographs unless the monographs are harmonized or there is a suitable rationale for the mixing of pharmacopoeial standards. The product should also meet all definitions in the pharmacopoeia and general chapter being used to determine criteria.

If applicants reference one of these pharmacopoeiae, then both the specific monograph and pharmacopoeia should be clearly identified. The most recent version of the relevant pharmacopoeia should also be sourced and referenced. Any additional testing that must be carried out should be clarified or the scientific justification as to why the additional testing is not required must be documented.

(iv) Amendments

Refer to the Amendments guideline

The Amendments guideline addresses the specific format to be used and content or documents to be provided for all amendments to the application, including responses to letters from the Authority, Authority resolutions/Committee recommendations, all pre- and post-registration amendment submissions. Pre- and post-registration amendments include all aspects of the application e.g. proprietary name, HCR/FPRR and/or Manufacturer, Packer, FPRC, Pharmaceutical and Analytical, Medicine Register Details.

The format is addressed in section 6: Format of the amendment schedule / covering letter. The types of pharmaceutical and analytical amendments that require or do not require prior approval are defined in section 5 and examples of data and other requirements provided in section 7.

(v) CTD headings

The headings used in this section follow the sequence of the International Conference on Harmonisation (ICH) guideline M4: ***Common Technical Document (CTD)***.

This section is divided into two subsections:

Module 3.2.S	Active Ingredient/s
Module 3.2.P	Pharmaceutical Product

Some complementary medicines are comprised of relatively simple ingredients (e.g. *single herb,* mineral salts) and, unless the medicine contains multiple active ingredients, the quality parameters applying to such products may be similar to pharmaceutical medicines.

However, complementary medicines that contain complex ingredients that are difficult to characterise and/or certain combinations of multiple active ingredients require special consideration.

The types of information and level of detail depend on the active ingredient(s) and on the risk associated with the product.

Information that should be provided includes the substance name, composition, structure (chemical and/or morphological where possible) and general properties; manufacturing details, including process and controls; substance characteristics, including impurities and incidental constituents; specifications and details of analytical test methods, with method validation data; stability data.

3.1 Table of contents (ToC) of Module 3

Provide a comprehensive table of contents (ToC) for Module 3 that includes a complete list of all documents provided in the application by module and at least lists all the relevant aspects addressed in the registration guidelines and/or the narrative headings of the CTD where relevant. A list of all the sections only does not facilitate review and does not suffice.

In the table of contents, the location of each document should be identified by referring to the volume numbers that contain the relevant documents and any tab identifiers. In general, the name for the tab identifier should be the name of the document (section heading according to the CTD format e.g. 3.2.P.4.2). If the full name of the document is too long for the tab identifiers, an alternative name that adequately identifies the document should be substituted.

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

3.2 Body of data

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

For a complementary medicine containing more than one active ingredient, the information required for part “S” should be provided in its entirety for each ingredient.

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

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

Provide the name of the substance. The approved name should be the same as the name reflected in Module 1.3. Any active ingredient name should be reflected as per Annex B.

Chemical Substance Name

The approved name i.e. International Non-Proprietary Name (INN) or chemical name of substances used must be stated. In the absence of such name being available, a chemical description or characterisation of the substance should be given.

The approved name (INN) or chemical name of mineral, metal or chemical substances or prepared mineral substances used in Homeopathic, Traditional Chinese, Ayurvedic or Unani Tibb medicines must be stated.

Biological Substance Name or Animal Substance Name

In addition to the name of the organism, the part, preparation and / or biological descriptor may be required to fully name a biological or animal substance.

Herbal Name

For purposes of the registration procedure, herbal names are stated in the Latin binomial format, which must include the genus, species, subspecies, variety, sub-variety, form, sub-form or chemotype and author where appropriate. Reference must be made to the internationally accepted name for the plant, fungus or alga by referring to the following databases where appropriate (in order of priority):

a) The Plant List (Available at: http://www.theplantlist.org)

b) The Index Fungorum (Available at: http://www.indexfungorum.org)

c) The International Plant Names Index (Available at: http://www.ipni.org) OR

d) Other recognised major flora

Examples of correct herbal names include:

- *Olea europaea* subsp. *africana* (Mill.) P.S. Green
- *Crataegus curvisepala* Lindm.
- *Thymus zygis* subsp. *gracilis* (Boiss.) R.Morales ct. thymol

Herbal Ingredient: The Latin binomial name (as above), the part and the preparation (including solvents and ratio if applicable) are used to fully name a herbal ingredient.
For purposes of labelling, a simple Latin binomial or pharmacopoeial names of herbal ingredients that are fully characterised in a monograph of an accepted pharmacopoeia may be used provided it is clear to the consumer exactly which herb (or part thereof) is being used.

Herbal Component Name (HCN)

HCNs are names for classes of constituents that are found in herbal ingredients. The need for a HCN most often arises when a herbal extract is standardised to a particular class of constituents, or where particular classes of constituents are restricted (e.g. hydroxyanthracene derivatives).
Where a herbal extract is standardised to a single constituent, the single constituent should have a chemical name. The HCN is not a stand-alone name and should be used only when expressing a herbal substance.

Other names

Common names, *Materia Medica* Names and/or Discipline-specific names (e.g.: Traditional Chinese Pin Yin, Traditional Sanskrit or Traditional Unani Tibb Names) may be used in addition to the approved names.
The Pin Yin name of the plant may also be used in addition to the English names of the plant parts in the case of Traditional Chinese medicines.

Homeopathic medicines

A definition of the homeopathic stock(s) and the homeopathic name(s) should be provided. For homeopathic stocks of herbal origin for example:

- Binominal scientific name of plant (genus, species, variety and author) and chemotype (where applicable)
- State (fresh or dried) and part(s) of the plant
- Other names (synonyms)/ homeopathic names /Latin names
- Reference of the homeopathic manufacturing procedure
- Description of vehicles used

3.2.S.1.2 Structure (name, manufacturer)

Where appropriate provide the chemical structure (graphic), molecular formula, molecular mass and Chemical Abstracts Service Registry (CAS) number for the substance, unless this is provided in the relevant monograph or standard.
For herbal substance/s and preparation/s the physical form and a description of the constituents with known therapeutic activity or markers (molecular formula, relative molecular mass, structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass) should be provided. Other constituents, if relevant, should be stated.

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

Provide any physico-chemical information relevant to the characterisation of the substance or that may be required for the manufacture, performance or stability of its intended final dosage form that is not covered by the relevant monograph or standard (e.g. solubility or particle size).

This information must be sufficient to:

- adequately characterise/describe the active ingredient(s);
- determine the shelf life *and*
- demonstrate that the active ingredient(s) will be of appropriate and consistent quality.

3.2.S.2 Manufacture (name, manufacturer)

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

State the name, business and physical address of all sites involved in the manufacture / testing of the ingredient/substance being applied for.

This includes each producer or supplier and each proposed site or facility involved in the production/ collection and testing of the herbal substance.

Where relevant, state the country or region of origin of the ingredient, or give other details such as time of harvesting and stage of growth, which are pertinent to the quality of the ingredient.

No active ingredient 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)*

*Refer to **Section 6** for a list of active ingredients where a method of synthesis is not required.*

Describe the manufacture of each active ingredient and include a flow chart of the manufacturing process.

State the part of the plant or animal used and the form used, i.e. whether fresh or dried material is used. Steps in the process should identify the appropriate process parameters, such as time, temperature or pH. State the batch size(s).

For a herbal substance, adequately describe the plant production and plant collection. Where relevant provide details pertinent to the quality of the ingredient, e.g. harvesting and stage of growth.

Describe any processing, including solvents, extraction, concentration, fractionation or other manipulation before use in the manufacture of the final product.

Indicate whether extractions alone or whether additives such as calcium phosphate in dry extracts, are present in the final product.

Describe the steps or controls taken to ensure that 'low dose' starting materials are of reproducible quality.

For substances having several manufacturers, provide the required information for 3.2.S.2.2 and 3.2.S.3.2 in its entirety for each manufacturer.

Relevant to homeopathic medicines:

The description of the homeopathic stock(s), intermediate dilutions and/or triturations and final dilution manufacturing process represents the applicant's commitment for the manufacture of the homeopathic stock(s) and final dilution. Information should be provided to adequately describe the manufacturing process and process controls. For example:

A sequential procedural narrative of the manufacturing process should be submitted. The narrative should include, for example, quantities of raw materials, solvents/vehicles, reagents (if applicable), critical steps and the controls that are intended to result in the routine and consistent production of material(s) of appropriate quality. A flow chart of the manufacturing process should be included. For homeopathic stock(s) and final dilution reference should be made to the appropriate section of a European Pharmacopoeia, or in absence thereof, to a homeopathic manufacturing procedure described in an official Pharmacopoeia of a Member State of the European Union.

The different stages of the preparation of the homeopathic stock(s) and final dilution or any preliminary treatment or transformation operation must be sufficiently described to allow the assessment of the consistency of the quality. The material, processes and specific precautions (light, moisture, miscellaneous contamination, and temperatures) must be described.

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

Provide information on the quality and control of the materials. Provide information to demonstrate that materials meet standards appropriate for their intended use, as appropriate.

For herbal preparations, list materials used in the manufacture of the herbal preparation, e.g. starting material, solvents, excipients, and identify where each material is used in the process.

Refer *to the SA Guide to GMP Annex 7 section 7.3.1 which addresses starting materials of active ingredients.*

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

Provide tests and acceptance criteria (with justification, including experimental data) carried out at critical steps identified in 3.2.S.2.2 of the manufacturing process to ensure that the process is controlled.

Provide information on the quality and control of intermediates during the process.

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

Provide process validation and / or evaluation studies (based on historical data), especially if it is a non-standard process, e.g. spray-dried products.

Include the decontamination process validation if necessary.

Include process validation and/or evaluation studies for aseptic processing and sterilisation. 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 herbal substance(s) and herbal preparation(s) provide a brief summary describing the development where applicable, taking into consideration the proposed route of administration and usage.

The comparability of the phytochemical composition of the herbal substance/herbal preparation used in supporting bibliographic data and the herbal substance/herbal preparation described in 3.2.S.1.2 should be discussed as appropriate.
For NCEs refer to ICH MQ4

3.2.S.3 Characterisation (name, manufacturer)

(Sometimes informally referred to as Compositional Information)

This is, in essence, a physicochemical definition of the substance(s).

Characterisation of simple complementary medicinal substances is usually straightforward and may be a simple extension of the specifications. For complex complementary medicines, the characterisation is generally more detailed and contains a significant amount of additional qualitative and quantitative data.

Where appropriate and possible, a major component (constituent) or marker compound of a substance should be determined. In addition, any major or minor constituents that have significant bearing on the action of the substance/product, should be determined only if the presence, absence or concentration of these compounds have any effect on the quality, safety or efficacy of the substance or product (e.g. the pulegone content of an essential oil or relative EPA/DHA concentration of a fish oil).

Many complementary medicine substances have yet to be defined or characterised in a monograph that is acceptable to the SAHPRA. Therefore specifications and control procedures that substantially characterise these substances should be proposed by the applicant.

In general, these should:

- sufficiently define the nature or character of a substance;
- allow the substance to be distinguished from adulterants, substitutes or counterfeit versions;
- be specific for components of safety and / or therapeutic significance;
- take into account the biological, chemical and physical variations that may reasonably occur between batches of the substance; and
- be capable of objective validation.

Data on the nature or chemistry of the active ingredient(s) should be provided. This may include citation of pharmacopoeial monographs, authoritative references, or in-house data that can be independently validated.

In addition, information on solubility (in water and other relevant solvents, such as dissolution media), particle size and polymorphic form (which are specific to complementary medicines) should be provided, where relevant.

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

For herbal substances, provide information on the botanical, macroscopical, microscopical, phytochemical characterisation, and biological activity if necessary.

For a non-compendial herbal substance, provide iconography of the plant and the part of the plant, and of the microscopical characters. Provide chromatographic profiles (TLC, HPLC, GC).

For herbal preparations, provide information on the phyto- and physicochemical characterisation, and biological activity, if necessary.

The phytochemical characterisation consisting of chromatographic profiles (TLC, HPLC, GC) is important to define the herbal substance and preparation, especially for the toxicological studies and clinical studies. The characterisation is sometimes made with additional chromatographic profiles (e.g. HPLC profiles in addition to TLC profile retained for routine testing).

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

Provide information on impurities and incidental constituents.

All herbal starting substances and intermediates must be free of contaminants.

The absence of orthodox pharmaceutical substances or chemicals must be confirmed.

The absence of herbal adulterants must be confirmed.

Information concerning impurities that are not dealt with in the monograph or standard reference should be provided. Different impurities may be present if the manufacturing process for the substance differs from the process for the substance upon which the monograph is based.

One of the key purposes of raw material specifications for complementary medicines is to determine whether the active raw material is free of contaminants that may have safety implications. Therefore, incidental constituents and impurities need to be considered and tests and limits included in the active ingredient specifications.

Impurities and incidental constituents are those constituents that may be present in a substance as a by-product of the production, processing or storage of a substance, and are immaterial to the nature of the substance.

The production, processing and storage of substances may result in the presence of impurities and incidental constituents; for example, micro-organisms, microbial toxins, radionuclides, metals and non-metals, pesticide residues, degradation products, general contaminants, solvent residues and manufacturing by-products. These constituents may be potentially hazardous to human health and their presence therefore needs to be minimised. Describe in detail the procedures adopted to achieve this.

Consider each type of likely impurity and incidental constituent, and determine whether it is relevant to the substance in question, including consideration of the following:

microbiological limits (moulds and bacterial endotoxins)

microbial toxins / mycotoxins e.g. aflatoxins, and ochratoxins;

radionuclides;

radiolytic residues;

metals and non-metals, e.g. lead, arsenic, selenium;

agricultural and veterinary chemicals, e.g. pesticides, fungicides;

general contaminants, e.g. dioxins, polychlorinated biphenyls;

solvent residues; and

manufacturing by-products, e.g. reagents, catalysts, co-extractives, degradation products.

3.2.S.4 Control of active pharmaceutical ingredient *(name, manufacturer)*
Control of Active Ingredient(s) / Substance(s) – Specifications and Analytical procedures

The active ingredient specifications are a set of tests and limits that are applied to the complementary medicine substance in order to ensure that every batch is of satisfactory and consistent quality. The specifications should monitor all parameters (generally by physico-chemical testing) where variation would likely affect the quality or safety of the product.

Appropriate testing techniques are required in accordance with the SA Guide to GMP Annex 7 – *Manufacture of Herbal Medicinal Products*. These need to cover identity and, where appropriate, adulteration and contamination, both chemical and microbiological. Where a herbal ingredient is standardised in terms of a component(s) and the statement of activity on the label is based on this standardisation, provide evidence of how the standardisation is achieved.

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

Provide comprehensive specifications (tests and limits) for each active substance.

The manufacturer of the active ingredient should apply specifications and control procedures for the substance at the time of its manufacture.

The final product manufacturer is also expected to ensure that the active ingredient complies with specifications before using it in the final product at the time of manufacture of the final product.

The two sets of specifications are not necessarily identical.

Include the specifications of the manufacturer of the active ingredient in tabulated form, not narrative, and those of the final product manufacturer, if different. Indicate clearly if these specifications are the same.

If there is a recognised pharmacopoeial monograph for the active substance, it must be used unless otherwise justified. Note that the most recent edition of any pharmacopoeial standard or monograph should be used, or a well-motivated justification for not doing so provided. The requirements of the recognised pharmacopoeiae or applicable general monographs in these pharmacopoeiae must also be met except where a justification for not doing so is sufficiently motivated by the applicant.

Where there is no pharmacopoeial reference for an ingredient, adequate specifications and control procedures must be included.

In some cases, the pharmacopoeial requirements may not in themselves be sufficient to adequately control the quality and consistency of an ingredient, in which case they may be expanded/additional tests may applied. However, it is generally not acceptable to:

- adopt only some of the tests from a pharmacopoeial monograph, without sufficient expert motivation;
- selectively combine some tests and/or limits from one specific pharmacopoeial monograph with some from another pharmacopoeial monograph (without having ensured full compliance with either);
- adopt an earlier edition of the pharmacopoeial monograph or standard when there is a more recent edition.

Where non-pharmacopoeial specifications are applied (e.g. European Food Standards Authority), a tabulated summary of the tests, test methods and limits should be provided *(e.g. assay (non-aqueous titrimetry): 99,0 – 101,0 %).* The specifications applied should be justified in respect of their ability to assure the quality and consistency of the ingredients used.

Similarly, where a pharmacopoeial monograph is used as the specification, justify any modification to the pharmacopoeial requirements.

For example:

- Permitted isolates and synthetic duplicates of materials of natural origin (e.g. flavonoids such as rutin and vitamins) should be identified at the raw material stage by physical description (e.g. colour, crystalline form, melting point or boiling point, optical rotation, etc.) and appropriate chemical identification tests such as infrared spectroscopy should also be performed. For

example, fish oils can be characterised by the fatty acid composition of the oil, acid value, anisidine value, peroxide value, total oxidation value, specific peak retention times from chromatography compared to a reference standard and/or any other appropriate identification tests.

- If the medicinal ingredient is an enzyme, characterisation includes details of the source organism. Additional details such as gel electrophoresis, substrate specificity, isoelectric point, specific activity should also be documented. Testing can be done according to pharmacopoeial methods or methods approved by the International Enzyme Commission.
- For probiotics where strain identification is necessary, a qualitative description of the probiotic culture should be provided. This includes identity parameters such as Latin binomial name (e.g. *Bifidobacterium adolescentis*) as provided for in Annexure C. The identity of probiotic strains should be determined unambiguously using the most current valid methodology, preferably by using a combination of phenotypic and genotypic methods. Strain identity should be verified routinely. Identification should ensure the absence of non-product bacteria at the raw material stage.

The specifications for the active ingredient should be guided by the characterisation / physicochemical definition.

In the case of fatty or essential oils used as active substances of herbal medicinal products, include a specification for the herbal substance unless justified.

A The minimum tests and limits included in specifications for an active ingredient include:

(i) appearance/description;

(ii) identification:

(a) Plants, fungi, seaweed, algae or lichens will generally be identified according to a suitable morphological and histological description system (such as the Angiosperm Phylogeny Group III system [APGIII] system) where acceptable reference specimens are used and must be named according to the internationally accepted standard [see 1.5.1 (iii)]. The parts of the plant that are used or the whole plant must be specified.

(b) Where the plant or other material is examined for the first time in a powdered or crude form, it must be subjected to at least macroscopic and microscopic examination. A detailed description of any organoleptic properties used to assist in the confirmation of the identity must be included.

(c) Where it is not possible to confirm the identity by macroscopic and/or microscopic examination, suitable identification tests or assays must be performed by comparing the specimen to reference substances or known active ingredients or markers.

(d) Where relevant, extracts for identification by suitable and validated methods should be made.

(e) For homeopathic medicines where Mother Tinctures or starting substances are prepared, the plant will be identified according to a suitable plant description and identification system (such as the Angiosperm Phylogeny Group III system [APGIII] system) where reference authentic specimens are used.
The identity of starting substances can, at Mother Tincture level, be established by means of suitable thin layer chromatograms which are congruent with reference chromatograms, or by other suitable methods. Thereafter product integrity and identity must be ensured by means of a carefully documented paper trail after positive identification by a suitably qualified person.

(f) 'Low dose' herbals are herbal extracts that are not manufactured to create standardized or higher levels of active ingredients in the extract. They are manufactured according to approved pharmacopoeiae or similar standard. They must be identified by a suitable description and identification system, where acceptable reference specimens and/or suitable and validated analytical methods are used.

(g) Therapeutic or pharmaceutical markers/active ingredients, can be used to identify standardized extracts or concentrates.

(h) Where materials other than plants are used, suitable systems and/or methods that are capable of confirming the identity of the substance must be employed.

(i) The identification of aromatherapy substances

- Appropriate methods or systems must be used to confirm the identities of the plants and the parts of plants used to manufacture the aromatherapy substance. For this purpose suitable plant description and/or identification systems must be used. Where plants are compared, reference to authenticated specimens may be made.
- Large variations, which are caused mainly by geographic and climatic variances may occur from batch to batch with respect to the active principles of aromatherapy substances. For this reason suitable plant description and/or identification systems should be used together with validated test methods and document trails.

(iii) content/assay;

Suitable pharmaceutical or therapeutic markers may be used in conjunction with suitable and validated test procedures to determine the concentration or strength of starting substances and/or final products.

Concentrations or quantities of scheduled substances must be specified and controlled within the Schedule limits.

If the quality of the herbal substance is specified in accordance with a monograph included in a recognised pharmacopoeia which does not include an assay, e.g. cinnamon, myrrh, gentian tinctures, reference to the monograph only is sufficient, it is not required to develop an assay for the herbal substance. Specifications of herbal preparations derived from herbal substances should include a suitable assay, the selection of appropriate constituents to serve as the basis for the assay will depend on the particular herbal preparation.

In exceptional cases, the assay can be replaced by other tests (e.g. bitterness value, swelling index).

(iv) impurities (e.g. residual solvents, heavy metals, synthetic impurities and degradants)

Define maximum limits for potentially toxic constituents and impurities of some herbal substances and/or preparations e.g. pyrrolizidinic alkaloids, essential oils containing safrole.

B Additional tests and limits

Additional tests and limits may be appropriate and will depend on the nature of the active ingredient. For example, tests for the presence or the proportion of isomers, optical rotation, microbial contamination, particle size distribution, and the clarity, colour and pH of solutions may also be relevant.

C Controls on the macro components

The specifications might also include controls on the macro components such as nitrogen content or sodium content. For complex liquid formulations, solvent content or viscosity might be important.

Additional simple tests that could assist in characterisation could include colour, texture, smell and pH. More complex or specific tests should be used where there is a need to determine a component in a

substance that is significant, such as sodium content in a sodium salt of a substance or gas chromatograph characterisation of key components in an oil.

D Significant minor components

Significant minor components of a substance (e.g. content of a specific alkaloid) are particularly important. These components are often pivotal to the nature and/or safety of the substance, and their identification and analysis requires the attention of the applicant. An acceptable starting point may be to use monographs for similar substances as a model and adapt them to the substance in question.

E Substances that are mixtures

Substances that are mixtures (e.g. synthetic polymers or fatty acid esters of glycerol) may require additional tests to control such aspects of the mixture as:
acid value;
iodine value;
saponification value;
viscosity;
density;
refractive index.

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

Provide detailed methods for quality testing.

Provide the analytical methods used in the specifications that demonstrate the suitability of the method for the material in question. The information should cover accuracy, precision, specificity (e.g. freedom from interference by degradation products and other likely impurities) and linearity. Validation data are not required for methods described in a SAHPRA -recognised monograph or standard.

Provide the test methods for all non-pharmacopoeial procedures.

For homoeopathic substances the identity of starting substances can, at Mother Tincture level, be established by means of suitable thin layer chromatograms which are congruent with reference chromatograms, or by other suitable methods. Thereafter product integrity and identity must be ensured by means of a carefully documented paper trail after positive identification by a suitably qualified person.

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

Provide the analytical method validation. The information should cover accuracy, precision, specificity (e.g. freedom from interference by degradation products and other likely impurities) and linearity. Validation data are not required for methods described in a SAHPRA-recognised monograph or standard.

Details of test methods and method validation data should be provided for all non-pharmacopoeial methods.

For impurities, quantitative analysis of pesticides residues must be validated on a suitable herbal matrix (according to the indication given in the European Pharmacopoeia in 2.8.13).

For aflotoxins determination (and ochratoxin A determination for herbal medicines subject to contamination), the suitability of the European Pharmacopoeia methods (2.8.18 and 2.8.22 respectively) to the herbal matrix tested must be carried out.

For microbiological examination, the suitability of the method must be carried out (according to the indication given in Ph Eur 2.6.31).

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

Submit valid Certificates of Analysis (CoAs) from the API manufacturer relating to at least two batches. A valid certificate of analysis is on an approved company letter head, signed and dated and complies with the requirements for documentation in chapter 4 on Documentation in the SA Guide to GMP.

If data on commercial-scale batches are not available, certificates of analysis should be provided for pilot-scale batches manufactured using the same process as intended for commercial-scale batches.

When there are several sites of production for a substance, provide the results of analysis of at least one batch per site.

When alternatives / different sites are described for the herbal preparation, provide the results of the analysis of the batches for each.

The results of the analysis are to be given as actual figures whenever possible instead of statements such as “conforms”, “complies”. In cases of use of TLC, a coloured photographic picture should illustrate the results.

Certificates of analysis should also be provided for any batches of material used in toxicity tests and clinical trials reported in support of the application. This will confirm whether or not the substance intended for sale is the same as that on which safety data have been provided. It is important that batch analysis data for the active ingredient are included for batches that were used in clinical trials submitted in support of the application.

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

Provide a justification for the specifications unless these are pharmacopoeial in which case this should be stated.

If an applicant proposes to use an alternative monograph or standard when a BP, Ph Eur or USP standard exists, a well-motivated justification for doing so is required. The justification should explain why the standard(s) cannot be met and detail what alternative(s) are proposed and why.

If there is no relevant monograph or standard for the active ingredient, a detailed justification for the proposed specifications should be provided. The justification should address the central function of the active ingredient specifications, which is to ensure the use of a consistently high-quality substance in the finished final product. Specifically, identification, assay, control of impurities and other critical factors in the quality of the active ingredient must be addressed.

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

Provide information on the reference standards or reference materials used for the testing of the substance / herbal substance and of the herbal preparation.

The composition of non-pharmacopoeial reference standards intended for use in assays should be adequately controlled and the purity should be measured by validated quantitative procedures.

For these non-pharmacopoeial standards, the supplier’s name and the standard reference number should be provided and storage conditions should be stated.

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

Provide a description of the container closure system, and the identity and specifications of materials of construction of each primary packaging component. Primary packaging components are those that are in direct contact with the final product providing protection.

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.

Non-compendial methods (with validation) should be included, where appropriate.

The suitability of the container 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) Refer to Annex Stability*

Provide stability data for the complementary medicine active ingredients.

Stability data must be provided for complementary medicine active ingredients to assist in, for example, identifying any particular degradants that may be formed and that must be monitored as part of the overall stability programme.

Stability data on new chemical entity APIs should be generated according to the Stability guideline.

Homeopathic substances

The following criteria shall apply with respect to shelf life and the determination of expiry dates:

(i) For D4 potencies upwards, with respect to products with single or multiple active ingredients, the shelf-life is consistent with the shelf-life of the vehicle substance containing the active potency.

(ii) Stability tests must be performed in accordance with Annex A: Stability Testing. Accelerated stability testing in the case of Homeopathic Substances is not appropriate in situations where the active substance(s) cannot be (accurately) identified in dilutions generally greater than D4).

(iii) For mother tinctures and potencies up to and including the D3 or 3x potency (or equivalent potency), stability testing should be done by means of Thin Layer Chromatography on the Mother Tincture, or on the potencies, where this is applicable and possible. Standardised reference extracts and thin layer chromatograms can be used for comparison purposes.

Relevant to stability testing of homeopathic products, for additional guidance refer to the Head of Medicines Agencies' "Points to consider on Stability Testing of HMPs".[1]

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

Summarise the types of studies conducted, protocols used and the results of these studies. Include conclusions with regard to storage conditions and re-test date or shelf-life, as appropriate.
Stress tests are usually considered not to be necessary for herbal preparations.

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

Provide the post-approval stability protocol and stability commitment stipulated in the Stability Annex.

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

Provide the results of stability studies in the prescribed format stipulated in the Stability Annex Presentation of Stability Data.

[1] Heads of Medicines Agencies: *Points to consider on Stability Testing of HMPs* https://www.hma.eu/380.html

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

The description of the final dosage form should be documented as part of the identification of the final product. Tests for identification of the final product might include tests such as organoleptic evaluation (sensory characteristics e.g., taste, odour, texture, appearance such as colour and shape of the capsule or tablet, etc.). Where the medicinal ingredient is a defined chemical entity, or where a marker is present, chemical identification tests (e.g., comparison of a retention time of a High Performance Liquid Chromatography (HPLC) peak with a standard) should be used.

A physical description of the final product should always be included in the final product specifications (e.g. clear colourless liquid, size 0 capsule red cap, blue body).

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

The table of ingredients required in this section should be provided per dosage unit or other suitable unit of mass or volume.

A description of the final product that includes the following information should be provided:

- table of the ingredients in the product and their quantity and purpose in the formulation (e.g. active, disintegrant, antimicrobial preservative) including solvents that are used, even if they are evaporated from the product during manufacture, and polishing agents that do not appear in the formulation;
- full/complete description of the dosage form, including any special character (e.g. modified release, film coated, uncoated);

The table of ingredients should provide greater detail than simply the product formulation. It should include overages (additional quantities of ingredients, over the amounts nominated in the product's formulation, added during manufacture) if any.

Components of a formulation are divided into active ingredients and inactive ingredients.

Ensure that the intended use of an inactive ingredient is appropriate and that it is used in appropriate amounts to achieve its technical purpose and that the inactive ingredient is approved for use as such.

Additives including Flavouring and Colouring Agents
Also refer to the Pharmaceutical & Analytical CTD (3.2.P.1) and Sugar Labelling Guidelines.

Complementary Medicines may not contain:

- any additive, colourant, flavourant, sweetener or preservative that is not permitted in foodstuffs *(refer to the Foodstuffs, Cosmetics, and Disinfectants Act, 1972 (Act 54 of 1972) or with directives of the EU or the register of the FDA);*
- any added fluoride in any form, or
- any additive which contains aluminium.

In addition, the sweeteners as stipulated in Tables 1-3 should be accompanied with clearly distinguishable and visible wording on the packaging indicating that the product "CONTAINS ARTIFICIAL SWEETENER <NAME OF SWEETENER(S)>".

The use of all artificial (non-nutritive) sweeteners are subject to the following further requirements:

1. Artificial sweeteners are not permitted for use in pre- or probiotic formulations, unless substantiated
2. Artificial sweeteners are not permitted in products intended for use in children younger than 36 months.

3. Artificial sweeteners are subject to the maximum permitted levels expressed as mg/l or mg/kg, as appropriate, as indicated in Tables 1-3 unless otherwise motivated:[2]

Table 1 Solid oral dosage forms including capsules and tablets and similar forms, excluding chewable forms

Artificial Sweetener	**Maximum level** *(mg/l or mg/kg as appropriate)*	**Additional Notes**
Acesulfame K	500	
Aspartame	2 000	
Cyclamic acid and its Na and Ca salts	500	Maximum usable levels are expressed in free acid
Saccharin and its Na, K and Ca salts	500	Maximum usable levels are expressed in free imide
Sucralose	800	
Neohesperidine DC	100	
Neotame	60	
Salt of aspartame-acesulfame	500	Limits are expressed as acesulfame K equivalent. The maximum usable levels are derived from the maximum usable levels for its constituent parts, aspartame (E 951) and acesulfame-K (E 950). The levels for both E 951 and E 950 are not to be exceeded by use of the salt of aspartame-acesulfame, either alone or in combination with E 950 or E 951.

Table 2 Liquid dosage forms

Artificial Sweetener	**Maximum level** *(mg/l or mg/kg as appropriate)*	**Additional Notes**
Acesulfame K	350	
Aspartame	600	
Cyclamic acid and its Na and Ca salts	400	Maximum usable levels are expressed in free acid
Saccharin and its Na, K and Ca salts	80	Maximum usable levels are expressed in free imide
Sucralose	240	
Neohesperidine DC	50	
Neotame	20	
Salt of aspartame-acesulfame	350	Limits are expressed as acesulfame K equivalent. The maximum usable levels are derived from the maximum usable levels for its constituent parts, aspartame (E 951) and acesulfame-K (E 950). The levels for both E 951 and E 950 are not to be exceeded by use of the salt of

[2] COMMISSION REGULATION (EU) No 1129/2011of 11 November 2011

Artificial Sweetener	Maximum level *(mg/l or mg/kg as appropriate)*	Additional Notes
		aspartame-acesulfame, either alone or in combination with E 950 or E 951.

Table 3 Syrups or chewable dosage form

Artificial Sweetener	Maximum level *(mg/l or mg/kg as appropriate)*	Additional Notes
Acesulfame K	2 000	
Aspartame	5 500	
Cyclamic acid and its Na and Ca salts	1 250	Maximum usable levels are expressed in free acid
Saccharin and its Na, K and Ca salts	1 200	Maximum usable levels are expressed in free imide
Sucralose	2 400	
Neohesperidine DC	400	
Neotame	185	
Thaumatin	400	
Salt of aspartame-acesulfame	2 000	Limits are expressed as acesulfame K equivalent. The maximum usable levels are derived from the maximum usable levels for its constituent parts, aspartame (E 951) and acesulfame-K (E 950). The levels for both E 951 and E 950 are not to be exceeded by use of the salt of aspartame-acesulfame, either alone or in combination with E 950 or E 951.

Modified Release Products

Refer to Dissolution and Biostudies Guidelines.

Controlled release claims of modified release formulation must be demonstrated by both physico-chemical data (dissolution data) and clinical data (bioavailability data) where appropriate.

Batch-to-batch variations in the quantity of ingredients

(i) Routine variations in inactive ingredients

It is recognised that it may be necessary to vary the quantities of certain inactive ingredients from batch to batch in order to achieve acceptable results during manufacturing.

Table 4 lists the changes to the nominal quantities of certain inactive ingredients that may be made in the manufacture of immediate release complementary medicines.

Table 4 Changes to the nominal quantities of certain excipients may be made as set out below.

Inactive ingredient type	Acceptable range around the nominal formulation
Quantity of ingredients whose function is to contribute to viscosity	+/– 10 %
Granulating fluid (fixed composition)	+/– 10 %
Disintegrant (even if the excipient serves more than one role in the formulation)	up to +25 %
Talc and water-soluble lubricants and glidants	–25 % to +100 %
Water-insoluble lubricants and glidants, except talc e.g. magnesium stearate, stearic acid)	+/– 25 %
Filler (bulking agent) in hard gelatin capsules	+/– 10 %
Carriers and potency-adjusting ingredients for materials of biological and herbal origin	+ /– 10 %
Filler (bulking agent) in tablets and soft gelatin capsules to account for the changes in the item above	+ /– 10 %

(ii) Variations in content of some active ingredients

For some active ingredients, such as herbal substances, the mass of the active raw material used in a batch of the formulated product may vary according to its composition.

Where the composition varies, fluctuations in the quantity of active raw material may affect the proportions of excipients present in the finished final product relative to the nominal formulation.

In some situations, the fluctuations in the mass of active raw material added may be compensated for by adjusting the quantity of a nominated excipient in order to maintain a target mass for the batch. This should be clearly identified in the application.

Batch-to-batch approval is not normally required. The formulation given in the application should indicate that the actual mass of active raw material will vary according to its estimated quantity., There should be an indication of which other inactive ingredients, if any, will be varied correspondingly, and the limits of the variation.

The reasons for proposed ranges in the quantities of any ingredients should be fully described in the product development summary. Validation data should be provided in Module 3.2.P.3.5 for the proposed ranges. Where the product is a tablet or capsule, the validation data should include dissolution or disintegration data, using the test method in the proposed finished final product specifications as defined in Module 3.2.P.5.

Overages

The use of an overage to compensate for poor analytical methodology or poor stability performance of the formulation is not sufficient justification.

If an overage (an additional quantity of an ingredient added during manufacture and greater than the quantity nominated in the product's formulation) is used during manufacture, details of the overage used should be included with reference to the maximum allowed overage limit.

The application's product development summary should include a justification for the proposed overage. This may take into account the inherent instability of certain ingredients.

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 information as detailed in the Guideline: Pharmaceutical & Analytical – CTD/eCTD.

It should contain information on the development studies conducted to establish that the dosage form, 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 the routine control tests carried out according to the specifications.

Additionally, this section should identify and describe the critical parameters i.e. formulation and process attributes that can influence batch reproducibility, product performance and quality.

Additional supportive data can be referenced to the relevant non-clinical or clinical sections of the dossier.

Where a medicine has modified release characteristics or an unusual method of manufacture, the product development summary should include a detailed discussion and justification of the development of those characteristics or method and any relationship with the final product specifications. For example, for an enteric-coated tablet, dissolution and formulation studies performed during development should be described and related to the dissolution test in the final product specifications.

If any overages are proposed, the developmental work that led to the proposed overage should also be discussed.

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 manufacture of the active substance(s).
Provide information on the compatibility of the active substance with excipients listed in 3.2.P.1. Additionally discuss the key physicochemical characteristics e.g. water content, solubility, particle size distribution, of the active substance that can influence the performance of the final product.

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

Discuss the choice of excipients listed in 3.2.P.1, their concentration and characteristics that can influence the final product performance relative to their respective functions.
Non-compendial excipients/IPIs should be avoided. Submit the safety/toxicity profile of the IPI is not compendial.

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

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

Provide a brief summary describing the development of the final product, taking into consideration the proposed route of administration and usage.

For herbal medicinal products, the comparability of the phytochemical composition of the products used in supporting bibliographic data and the product described in 3.2.P.1 should be discussed, where appropriate.

Refer to Guideline: Pharmaceutical & Analytical – CTD/eCTD

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

Justify any overages in the formulation described in section 3.2.P.1

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

Discuss parameters relevant to the performance of the final product, e.g. dissolution and/or disintegration for solid oral dosage forms, pH for solutions.

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

Explain the selection and optimisation of the manufacturing process described in 3.2.P.3.3, in particular critical aspects. 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)*

Discuss the suitability of the container closure system described in 3.2.P.7 used for the storage, transportation (shipping) and use of the final product. 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 discuss the microbiological attributes of the dosage form 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*.

Relevant to microbial limits in homeopathic products, for additional guidance refer to the Heads of Medicines Agencies' "Points to consider on the selection of microbial limits for non-sterile homeopathic raw materials, stocks, preparations and products".[3]

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

Address the compatibility of the final product with the reconstitution diluent(s) or dosage device(s) if relevant.

3.2.P.3 Manufacture (name, dosage form)
Licensing and Control

The manufacturer's licence carries details of the types of manufacture permitted under the licence. Where a product is imported, each nominated overseas manufacturer is expected to demonstrate an acceptable standard of GMP. *Refer to SA Guide to GMP.*

[3] Heads of Medicines Agencies: *Points to Consider on selection of Microbial limits for non-sterile homeopathic raw materials, stocks, preparations and products* https://www.hma.eu/380.html

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

Provide the name, physical address and responsibility of each manufacturer and each proposed production site or facility involved in the manufacturing, packaging and testing of the product.

Details of the manufacturing process for the final product should be provided for each manufacturing site. These steps should include the manufacture of the dosage form, packaging and labelling, chemical and physical testing, microbiological testing and release for sale.

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 carried out 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)

Provide 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.

A batch formulation should be provided in table format. It should include all of the components that will be used in the manufacture of the final product and their quantities on a per batch basis (including any overages), correlated to the unit formula.

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

Provide a description and comprehensive flow diagram of the manufacturing process, including packaging and in-process controls that represent the sequence of the steps undertaken and the scale of production.

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.

The manufacturing details should include information about:

- solvents that are used, even if they are evaporated from the product during manufacture;
- polishing agents that do not appear in the formulation.

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

Include 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.

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.

When an intermediate is not used immediately, the condition of storage (e.g. packaging, temperature, holding time) should be described and supportive documentation provided.

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.

Provide tests and acceptance criteria (with justification including experimental data) carried out at the critical steps identified in 3.2.P.3.3 of the manufacturing process, to ensure that the process is controlled.

For intermediates details of all control tests, with details of test procedures and limits applied at any intermediate stages of the manufacturing processes, are required, especially if these tests cannot be carried out on the herbal medicinal product and supported by the documentation.

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

Submit a process validation protocol (VP) or report (VR) (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.

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 in 3.2.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 must 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)*

Provide specifications for inactive ingredients (excipients). Also refer to 3.2.S.4.1 above

All ingredients in complementary medicines, including inactive ingredients, should have suitable specifications.

If there is no relevant monograph or standard for an inactive ingredient, full details of the specifications for each excipient are required.

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 Authority. 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.

(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.

(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.

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

Provide the analytical procedures used for testing the inactive ingredients (excipients).

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)*

Provide analytical validation information where appropriate.

Details should be provided of all analytical methods used in the specifications, together with validation data that demonstrate (among other things) accuracy, precision, specificity (e.g. freedom from interference by degradation products and other likely impurities), and linearity.

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

Provide justification for the proposed excipient specifications, where appropriate.

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

Declare any excipients of human or animal 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 in 3.2.R.6.

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

Provide information on any excipients used for the first time or by new route of administration.

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. (Provide details in 3.2.A.3)

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

The final product specifications are a set of tests and limits that are applied to the final medicinal product in order to ensure that every batch is of satisfactory and consistent quality at release and throughout its shelf life. The specifications should be used to monitor all parameters (generally by physico-chemical testing) where variation would be likely to affect the quality, safety or efficacy of the product.

The specifications against which a finished final product is tested before release for sale are referred to as the “batch release” specifications in this document; those against which the product is tested to ensure satisfactory quality throughout its shelf life are referred to as the stability specifications.

The final product specifications should be provided, defining the physical, chemical and microbiological characteristics of the product and detailing quality-control test methods and test specifications.

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 in 3.2.P.3.3 a 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.

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.

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

Provide tabulated release and shelf-life specifications for the product.

Release and stability specifications must be tabulated separately.

Tighter limits are usually applied at batch release to critical parameters to allow for possible changes to the product during storage (e.g. decomposition of the active ingredient).

The batch release limits must be chosen in order to guarantee that all batches will comply with the expiry specifications throughout the product's shelf life.

As a minimum, the stability specifications should include all of the relevant tests in the batch release specifications.

Identification

The final product must be identified by accepted pharmacopoeial methods or, when not available, by validated in-house methods. Product identification must be supported by a carefully documented paper trail.

Assay

Suitable pharmaceutical or therapeutic markers may be used in conjunction with accepted and validated test procedures to determine the concentration or strength of starting substances and/or final products.

Concentrations or quantities of scheduled substances must be specified and controlled within the limits stated for a specific Schedule.

Quantification by Assay

Quantification by assay is a method for determining the presence or quantity of a component or ingredient against which a therapeutic claim is made.

In the case of medicinal ingredients that are single chemical entities, those that contain a constituent that is used to standardize a product, or for those who have a known biological activity, quantitative assay tests can be done at the final product stage according to appropriate analytical methods described in the pharmacopoeiae (e.g. USP, Ph. Eur.).

Botanical ingredients including extracts

Specific marker compounds may be assayed in whole herbs and extracts of botanical ingredients. If no pharmacopoeial standard is available for assaying the marker, then it is the product licence holder's responsibility to determine appropriate limits for the marker based on data on safety and efficacy of the product and natural variability of the marker.

Quantitative tests for a particular component in an extract can be done at either the final product stage or at the extract ingredient stage using appropriate analytical methods. If the evidence supporting a claim is based on the quantity of a particular active component, then quantification of that component should be performed at the final product stage. When a marker compound is declared on the PLA and the label tolerance limits for quantification should be set such that there is an upper and a lower limit.

When the component that is analysed is found in several ingredients in the product, then the total amount of the component should be reflected on the label and specifications should be set to reflect the total amount from all sources.

Tolerance limits above 120 % may be used if scientifically justified. Safety of higher limits and degradation products should always be considered.

Vitamins and minerals

For vitamins, quantitative tests should be done on the finished product according to appropriate analytical methods described in an acceptable pharmacopoeia or other internationally accepted

methods. Tolerance limits for the quantity of vitamins and minerals should be as per USP limits for the individual vitamins and minerals but not exceed the stipulated limits in annexures. In the absence of a pharmacopoeial standard, licence holders should have a scientific rationale for quantities that are outside the general tolerance limits of 80 -120 %. It is recommended that the lower limit for the assay be set at 90 % of the label claim to ensure an appropriate amount of the medicinal ingredient at the expiry date.

Overage is used to compensate for the loss of vitamins and minerals during manufacture of the product or loss/degradation of vitamins and minerals during shelf-life of the finished product.

Isolates and synthetic duplicates

When ingredients are isolates or synthetic duplicates and no pharmacopoeial standard is available, tolerance limits of 80 to 120 % of the label claim are generally appropriate. The safety of degradation products should be taken into account when considering the expansion of tolerance limits.

Enzymes

The quantity per dosage unit must include the activity of the enzyme. Tolerance limits for the activity of enzymes should be 80 % to 150 % of the label amount. The activity is measured according to the reaction catalysed by individual enzymes (substrate specificity).

Methods and units (e.g. FCC Lipase Units, FCC Lactase Units) specified in the USP Food Chemicals Codex (FCC) should be used. Quantitative tests for a particular component in an extract can be done at either the finished product stage or at the extract ingredient stage using appropriate analytical methods. If the quantity of an enzyme is declared by mass, the activity should be declared as a potency. It is the responsibility of the applicant to ensure that all products meet a minimum of 80 % of the label claim for potency/activity at the end of the shelf-life.

Live microorganisms

Enumeration of live microorganisms should be performed using selective culture methods at the raw material and/or at the finished product stage. The total count of the cells should be expressed as colony forming units (CFU) per gram or per ml.

In the case where the medicinal ingredient is a blend of microorganisms it is acceptable to list the total CFU count as the quantity and list the strains as sources of the medicinal ingredient.

Applicants should ensure that all products do not contain less than 1 x 109 CFU per dose of viable organisms at the end of the shelf-life. Upper limits for total CFU's should be specified and justified. Evidence of the stability of that culture, under the recommended storage conditions, must be provided up to the end of the product's shelf-life.

Quantification by input

Quantification by input means that the active ingredients (against which no therapeutic claims are made) are not assayed at the final product stage. The objective evidence that the quantity of a medicinal ingredient (e.g., a plant material) has been added to the final product is calculated using the manufacturing batch record controlled by appropriate application of GMPs and in-process controls. Generally, the quantity of a medicinal ingredient is expressed as the targeted weight (e.g., mg) of the processed substance in each unit of the dosage form. It is the responsibility of the licence holder to ensure that quantification by input is appropriate for the ingredient.

Quantification by input may be appropriate when the active ingredient is a whole herb or a complex extract. In the case of medicinal ingredients where the formulation of the product is of such

complexity that a validated assay method for the quantity of an ingredient is unavailable or difficult to achieve (e.g. there is no published method of analysis for the medicinal ingredient, or the non-medicinal ingredients interfere with analysis), quantification by "input" may be considered to be acceptable.

It may also be acceptable to quantify an ingredient by input for a multi-ingredient product (e.g. multi-vitamin mineral products). In this case controls other than assay for some of the ingredients present, and assays of critical ingredients e.g. at minimum the least water soluble plus the most unstable vitamin may be used.

Raw material specifications for the medicinal ingredient(s) to be quantified by input should be comprehensive to ensure that adequate control of the medicinal ingredient(s) occurs. Standard operating procedures (SOPs) and batch records should clearly document the controls that are in place during manufacturing to ensure an adequate amount of medicinal ingredient is added to the mix during processing to achieve the labelled quantity per dosage unit. These documents should indicate the target quantity for the medicinal ingredient (i.e. 100 % of the label claim) and include controls on mass variation during tabletting or encapsulation.

Generally a 5 % mass variation for individual dosages is acceptable.

A description of how batch homogeneity will be controlled if more than one medicinal ingredient is mixed, or if the medicinal ingredient is mixed with non-medicinal ingredients, should be provided.

Dissolution and Disintegration *Refer to the Dissolution guideline for dissolution testing reporting and requirements*

Dissolution and disintegration may be indicators for bioavailability and are then considered an important characteristic of quality control for solid oral dosage forms.

Modified release products must include dissolution testing in the finished final product specification.

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 Authority.

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. Soft gelatine capsule preparations of dietary supplements meet the USP pharmacopoeial requirements for Disintegration.

If dissolution is performed it must be in accordance with the requirements of the latest USP/Ph.Eur. If, however, specific claims are made for specific vitamins and/or minerals or if the product contains other medicinal ingredients for which specific claims are made, the dissolution rate of such ingredients should also be determined in addition to e.g. the general USP dissolution requirements:

The general dissolution requirements for vitamin-mineral dosage forms include:

- Water-soluble vitamins: One index vitamin; folic acid (if present)
- Water-soluble vitamins with minerals: One index vitamin and one index element; folic acid (if present)
- Oil- and water-soluble vitamins: One index water-soluble vitamin; folic acid (if present)
- Vitamins with minerals: One index water-soluble vitamin and one index element; folic acid (if present)

- Minerals: One index element
- Oil-soluble vitamins only: Dissolution is not applicable.

In the absence of folic acid, the least water soluble plus most unstable vitamin may be used as index vitamin.

Impurity Requirements for Non-pharmacopoeial Products

The specifications for final products for which there is neither a BP, Ph. Eur. nor USP monograph for a closely related final product, should include tests and limits for impurities related to the active ingredient.

For impurity limits, the results of stability studies should be taken into account and reference should be made to information on toxicity. Specifically, the quantity and types of impurities that were detected in the stability studies should be consistent with the stability specifications and the proposed shelf life.

Consideration also needs to be given to the materials examined in the toxicity studies so that the product is consistent with the submitted safety data.

Unless otherwise stipulated by the SAHPRA for a particular product, limits on impurities in finished final products apply to impurities from all sources except water.

Residual Solvents

Solvent residues may be present in the active ingredient(s), inactive ingredients and may result from the manufacture process. Depending on the quantities and types of solvent residues from each of these sources, it may be appropriate to include a test and limits for residual solvents in the finished final product specifications.

Microbiological Requirements

Sterile Products

Generally, products that are required to be sterile will require extremely stringent microbiological specifications together with detailed information on manufacturing steps that ensure sterility.

Non-Sterile Products

All non-sterile dosage forms should include limits for microbial content in the finished final product batch release and stability specifications.

Products with significant water content (e.g. creams, gels and oral liquids) are likely to support microbial growth. Such products should include tests and limits for microbial content in both the batch release and expiry specifications.

For products containing an antimicrobial preservative, both the batch release and stability specifications should include physico-chemical tests and limits for content of preservatives. As the effectiveness of many preservatives is pH dependent, the specifications for such products should usually include requirements for pH that will ensure preservative efficacy. The stability limits for the preservative should be supported by preservative efficacy testing that is performed during stability testing.

If animal-derived proteins are used as raw materials or in the manufacturing process, there must be evidence of no risk of transmitting infectious viral agents, prions (such as BSE) or effective viral inactivation or removal in the manufacturing process.

Antimicrobial Ingredients

Antimicrobial preservatives are ingredients added to dosage forms to protect them from microbiological growth and associated degradation. The effectiveness of antimicrobial protection must be demonstrated for antimicrobial preservatives. Test methods used and tolerance limits should be as specified in an acceptable Pharmacopoeia (e.g. current USP <51>; Ph. Eur. 5.1.3), and should be performed on the final dosage form with suitable limits included.

The concentration of the preservatives shown to be effective in the final dosage form should be below a level that may be toxic to human beings, and should be at the lowest concentration necessary to preserve the product.

Preservative efficacy

The preservative efficacy of relevant dosage forms and/or presentations, e.g. multi-dose vials, eye drops should be specified in 3.2.P.5.1 and 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

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.

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

Physical characteristics of dosage forms

At least the following physical and other properties additional to those listed in the Stability Annex, 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 gelatine 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.

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

Provide analytical procedures used for testing of the product other than those from a recognised pharmacopoeia and include calculations 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)*

Provide analytical validation information, including experimental data, for the analytical procedures used for testing of the product.

Details should be provided of analytical method validation data that demonstrate (among other things) accuracy, precision, specificity (e.g. freedom from interference by degradation products and other likely impurities), and linearity.

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.

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).

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

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.

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.

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

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)*

When different / alternative sites are described in the dossier, the results of analysis of the batches should be provided for each.

Note that the results of the analysis are to be given as actual figures whenever possible, instead of statements such as “conforms” or “complies”.

At least two certificates of analysis for the final product to demonstrate compliance with batch release specifications must be provided. These certificates should relate to one or more production batches of the medicine or to trial batches if production batches have not been manufactured.

In such a case, the applicant should identify any differences between the trial process and the manufacturing process. The batch certificate for the trial batch, as well as the first production batch (if available) must be submitted.

For imported products, each batch must be accompanied by a Certificate of Analysis and an identification and assay test must be performed locally before such a batch is released for sale in order to demonstrate that product integrity has not been prejudiced during transit, unless exemption from this requirement has specifically been granted by the Authority.

If the transport method is appropriately monitored and the transport complies with the storage conditions, then only a description and an identification test by the importer are required. Exemption from these requirements may be considered per product.

Quantification in analysis may take place by assay or input.

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

Provide information on the characterisation of impurities if not previously provided in 3.2.S.3.2.

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

Provide justification of the final product specifications.

The suitability and acceptability of the tests, limits and test methods proposed for the final product should be justified with reference to the results of the method validation studies and the ability of the specifications to guarantee the quality and consistency of the final product.

A detailed commentary or justification for any unusual features in the final product specifications must be included.

The limits applied at batch release should be justified in terms of their ability to ensure that the product will remain within the expiry specification throughout its shelf life. For example, if the batch release and stability limits for assay are identical, the implication is that there will be no loss of the active ingredient throughout the shelf life. Any changes or unusual variability in the results obtained in the stability studies require adequate explanation.

The reasons for proposed ranges in the quantities of any ingredients should be appropriately outlined and justified in the application.

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

Provide information on the reference standards or reference materials used for testing of the product. 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*)

Provide a description of the container closure system, and the identity and specifications of materials of construction of each primary packaging component, as well as wadding and any other component in direct contact with the product, where applicable.

Sketches of containers for oral dosage forms and blister packs are not required.

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

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.

The suitability of the container should be justified in terms of its compatibility with the product and its ability to protect the product physically and also in protecting it from moisture and light should be addressed in Module 3.2.P.2.

For non-functional secondary packaging components, such as those that neither provide additional protection nor serve to deliver the product, only a brief description is required. e.g. outer cardboard carton.

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 if more than 25 % of the approved shelf life.

All pack sizes should be described in the submission.

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.

Child-protective measures must be employed with regard to the retail sale of salicylates 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)* *refer to **Annex Stability***

The purpose of the stability study is to establish, based on testing of the prescribed minimum number of batches of the final product, a shelf-life and label storage instructions applicable to all future batches of the final product manufactured and packaged under similar conditions. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout its shelf-life.

All applications to register a complementary medicine must include stability data for the proposed final product. The stability data must be sufficient to demonstrate, or indicate with a high probability, that the product intended for market will remain safe, of consistent quality and efficacious throughout the product's shelf life. The stability data will form the basis for setting a shelf life and recommended storage conditions for the product.

The maximum permitted shelf-life is generally five years unless specifically scientifically justified. Shelf life extensions of specific batches beyond the approved shelf life may be applied for with the supporting data in accordance with the Amendments guideline Type C category 19 (batch specific shelf life extension). Shelf life extensions of a product may be applied for in accordance Amendments guideline Type C category 10. Unless an active ingredient is inherently unstable, a shelf life of less than 24 months is not generally considered.

Homeopathic medicines

(i) For D4 potencies upwards, with respect to products with single or multiple active ingredients, the shelf-life is consistent with the shelf-life of the vehicle substance containing the active potency.

(ii) Stability tests must be performed in accordance with the Stability Guidelines. Accelerated stability testing in the case of Homeopathic Substances is not appropriate in situations where the active substance(s) cannot be (accurately) identified in dilutions generally greater than D4).

(iii) For mother tinctures and potencies up to and including the D3 or 3x potency (or equivalent potency), stability testing should be done by means of Thin Layer Chromatography on the Mother Tincture, or on the potencies, where this is applicable and possible. Standardised reference extracts and thin layer chromatograms can be used for comparison purposes for retesting purposes.

Relevant to stability testing of homeopathic products, for additional guidance refer to the Head of Medicines Agencies' "Points to consider on Stability Testing of HMPs".[4]

Aromatherapy

The stability of aromatherapy products/substances and expiry dates may be related to the stability of the vehicles and/or excipients.

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

Provide a summary of the types of studies conducted, protocols used and the results of the studies. 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)*

Provide the post-approval stability protocol and stability commitment.
Refer to the Annex Stability

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

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

For presentation of the stability data, refer to the Annex: Stability, section 4 Presentation of Stability Data.

3.2.A APPENDICES - not applicable

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

This Module addresses the pharmaceutical and/or biological availability / equivalence of the product. Refer to the PA CTD guideline if applicable to the submission.

3.2.R.1.1 Overview

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

3.2.R.1.3 Certificates of Analysis

[4] Heads of Medicines Agencies: *Points to consider on Stability Testing of HMPs* https://www.hma.eu/380.html

3.2.R.1.4 Pharmaceutical availability studies

3.2.R.2 Parent API manufacturer with various sites

This information is required if the manufacturer of the active substance uses more than one of its own sites.

If an identical route of synthesis, 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 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)

This information is required when a CEP or WHO CPQ is submitted in lieu of the API file in 3.2.S
Refer PACTD 3.2.R.3

3.2.R.4 Multiple API manufacturers

This information is required if the active substance is manufactured by more than one different manufacturers.

If more than one manufacturer of the active substance 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:

For more than one manufacturer of the active substance 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 active substance 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 active substance reported on in 3.2.R.4.2

3.2.R.5 Medical device

Not applicable

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 *Reserved for future use*

3.3 Literature references

Provide key literature references, if applicable.

4 TERMINOLOGY

Acceptance criteria

Numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures.

Active pharmaceutical ingredient / active substance

A substance or compound that is intended to be used in the manufacture of a complementary medicine as a therapeutically active ingredient that is responsible for its physiological or pharmacological action which may include a whole substance such as a single herb.

Characteristic constituents

Chemically defined substances or groups of substances that are specific for a medicinal plant and can be used for identification purposes.

Constituents with known therapeutic activity

Chemically defined substances or groups of substances which are generally accepted to contribute substantially to the therapeutic activity of a herbal substance, a herbal preparation or a herbal medicinal product.

Degradation product

Any impurity resulting from a chemical change in the composition of the active substance brought about during manufacture and/or storage of the active substance/ medicinal product by the effect of, e.g. light, temperature, pH, water, or by reaction with an excipient and/or the immediate container closure system. Due to the particular nature of herbals, for herbal substances/ herbal preparations/ herbal medicinal products in general only toxicologically relevant degradation products must be specified.

Drug extract ratio (DER)

The ratio between the quantity of herbal substance used in the manufacture of a herbal preparation and the quantity of herbal preparation obtained. The number (given as the actual range) written before the colon is the relative quantity of the herbal substance; the number written after the colon is the relative quantity of the herbal preparation obtained.

Excipient refer to / Inactive pharmaceutical ingredient (IPI)

Expiry / Expiration Date

The date placed on the container/label of a product designating the time during which a batch of the product is expected to remain within the approved shelf-life specification, if stored under defined conditions and after which it should not be used.

Extraction solvents

Solvents which are used for the extraction process.

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. i.e. The dosage form in the final immediate packaging intended for marketing.

Genuine (Native) herbal preparation

Genuine herbal preparation refers to the preparation without excipients, even if for technological reasons the genuine herbal preparation is not available. However, for soft and liquid herbal preparations the genuine herbal preparation may contain variable amounts of (extraction) solvent.

Ratio of herbal substance to genuine herbal preparation (DER genuine)

DER genuine is the ratio of the mass of the herbal substance to the quantity of the resulting genuine herbal preparation. The number (given as the actual range) written before the colon is the relative quantity of the herbal substance; the number written after the colon is the relative quantity of the herbal preparation obtained.

No matter whether the extract is prepared from a dry or a fresh herbal substance, the quantity of the herbal substance should simply be the quantity used, i.e. including any water naturally contained in the herbal substance.

The quantity of the native extract should be set as the quantity obtained after the extraction process, i.e. including any water and other solvent present in the extract, but without the quantity of any excipient added after the extraction process (excipients used for standardisation or technological reasons).

Due to the natural variability of the herbal substance, the DER genuine will normally be a range, e.g. 3,0-5,5:1. In the case of tinctures, where all of the extraction solvent is maintained in the final extract, the DER genuine will equal the drug extract ratio.

Likewise, the declaration of the extraction solvent should be based on the concentration of the solvent used, without taking any water naturally contained in the herbal substance into account.

Example: An extraction solvent prepared as a mixture of 5 000 kg ethanol 94 % m/m plus 1 000 kg purified water means that the declared solvent should be ethanol 78 % m/m.

Herbal medicinal product

A herbal medicinal product is any medicinal product, exclusively containing as active substances one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations.

Herbal preparations

Herbal preparations are obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates.

Herbal substances

Herbal substances are all mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried form but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author).

Herbal teas

Herbal teas consist exclusively of one or more herbal substance(s) intended for oral aqueous preparations by means of decoction, infusion or maceration. The preparation is prepared immediately before use. Herbal teas are usually supplied in bulk form or in sachets.

Impurity

1) Any component of the herbal substance, which is not the entity defined as the herbal substance.

2) Any component of the herbal preparation/herbal medicinal product that is not the entity defined as the herbal substance/preparation or an excipient in the herbal preparation/herbal medicinal product.

Impurities can be classified as follows:

- impurities arising from starting materials (active substances, excipients) and containers;
- process related impurities arising from the manufacturing process.

In addition, for herbal medicinal products the following groups of impurities should be addressed, if appropriate:

Contaminants, which are impurities such as heavy metals, pesticides, mycotoxins, fumigants as well as microbial contamination, including those arising from extraneous sources, and radioactive substances, if relevant.

Degradation products, which in the context of this Guideline, due to the particular nature of herbal medicinal product, should primarily address toxicologically relevant impurities arising from degradation of herbal substances/preparations.

*Residual solvent*s, which are impurities arising from manufacturing processes.

Inactive pharmaceutical ingredient (IPI)

A substance or compound that is used in the manufacture of a complementary medicine that 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.

Markers

Markers are chemically defined constituents or groups of constituents of a herbal substance, a herbal preparation or a herbal medicinal product which are of interest for control purposes independent of whether they have any therapeutic activity. Markers serve to calculate the quantity of herbal substance(s) or herbal preparation(s) in the herbal medicinal product if the marker has been quantitatively determined in the herbal substance or herbal preparation.

There are two categories of markers:

Active markers are constituents or groups of constituents which are generally accepted to contribute to the therapeutic activity.

Analytical markers are constituents or groups of constituents that serve for analytical purposes.

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.

Other extracts

Extracts essentially defined by their production process (state of the herbal drug to be extracted, solvent, extraction conditions) and their specifications.

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.

Quantification

Quantification means adjusting the herbal preparation to a defined range of constituents exclusively achieved by blending different batches of herbal substances and/or herbal preparations (e.g. quantified extract).

Quantified extracts

Extracts adjusted to a defined range of constituents (active markers).

Refined extracts

Standardised or quantified extracts submitted to purification procedures that increase the typical proportions of characterised constituents in the extractable matter with respect to the values expected by means of the extraction with a given solvent.

Refining

Purification of quantified or standardised extracts, which increases the typical proportions of characterised constituents in the extractable matter with respect to the expected values of pharmacologically or therapeutically active constituents obtained by means of the extraction with a given solvent.

Release Specification

The combination of physical, chemical, biological, and microbiological test requirements that determine whether a product is suitable for release at the time of its manufacture.

Shelf-life/Expiration Dating Period

The time interval that a product is expected to remain within the approved shelf-life specifications, provided that it is stored under the conditions defined on the label in the proposed container and closure system.

The shelf-life is used to establish the expiry date of individual batches. It is the length of time required for:

- the least stable API to degrade to the specified, motivated and approved or proposed, fraction of the labelled quantity,
- some element of pharmaceutical elegance to drop to an unacceptable level, or
- an arbitrary minimum of two years, unless otherwise determined by Authority.

The shelf-life could also reflect the length of time required for:

- a measurable increase in toxicity, as shown by either animal experiments or clinical adverse reaction reports, or
- a measurable loss in reported clinical effectiveness(even though analytical methods show little or no reduction in apparent concentration).

Shelf-Life Specification

The combination of physical, chemical, biological and microbiological test requirements that an API should meet up to at its retest date or a product should meet throughout its shelf-life.

Stability-Indicating Assay Methodology

Analytical method(s) that will quantitatively differentiate between the API and all known degradation products and/or related impurities.

Stability

The capacity of an API or dosage form to remain within specifications established to assure its identity, purity, strength and critical physico-chemical characteristics.

Standardised extracts

Extracts adjusted within an acceptable tolerance to a given content of constituents with known therapeutic activity.

Solvent

A solvent is an inorganic or an organic liquid used for the preparation of solutions or suspensions in the manufacture of a herbal preparation or the manufacture of a herbal medicinal product.

Specification

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 a herbal substance/preparation or herbal medicinal product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the herbal substance/preparation and/or herbal medicinal product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are binding quality standards that are agreed to between the SAHPRA and the applicant.

Specific test

A specific test is a test which is considered to be applicable to a particular herbal substance/preparation or a particular herbal medicinal product depending on their specific properties and/or intended use.

Standardisation

Adjusting the herbal substance/preparation to a defined contents of a constituent or a group of constituents with known therapeutic activity respectively either by adding excipients or by blending batches of the herbal substance and/or herbal preparation (e.g. standardised extracts

Storage Conditions

An acceptable variation in temperature and relative humidity of storage facilities. The equipment should be capable of controlling temperature to a range of ± 2 °C and Relative Humidity to ± 5 % RH. The real temperatures and humidities should be monitored during stability storage. Short-term spikes due to opening of doors of the storage facility are accepted as unavoidable. The effect of variations during equipment failure should be addressed by the applicant and reported, if judged to impact stability results. Exceptions that exceed these ranges (i.e. greater than 2 °C and/or 5 % RH) for more than 24 hours, should be described in the study report and their impact assessed.

Strength

A quantitative measure of API, as well as other ingredients, requiring quantification.

TAMC

Total aerobic microbial count.

TYMC

Total combined yeasts and moulds count.

Unidentified impurity

An impurity which is defined solely by qualitative analytical properties, (e.g., chromatographic retention time).

Universal test

A test which is considered to be potentially applicable to all herbal substances/preparations, or all herbal medicinal products; e.g. appearance, identification, assay, and impurity tests.

5 REFERENCES

in addition to SA guidelines listed under Introduction

1) Guideline on quality of herbal medicinal products/traditional herbal medicinal products (EMA/HPMC/201116/2005 Rev 2 / EMA/CPMP/QWP/2819/00 Rev. 2)
2) Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products (EMA/HMPC/162241/2005 Rev. 2 / CPMP/QWP/2820/00 Rev 2).
3) Guideline on quality of combination herbal medicinal products / traditional herbal medicinal products (EMEA/HMPC/CHMP/CVMP/214869/2006)
4) Reflection paper on markers used for quantitative and qualitative Analysis of herbal medicinal products1 and traditional herbal Medicinal products (EMEA/HMPC/253629/2007)
5) Guideline on good agricultural and collection practice (GACP) for starting materials of herbal origin. (EMA/HMPC/246816/2005)
6) Questions & answers on quality of herbal medicinal products/traditional herbal medicinal products1 (EMA/HMPC/41500/2010 Rev.5)
7) Note for guidance on development pharmaceutics CPMP/QWP/155/96

6 LIST OF ACTIVE INGREDIENTS WHERE A METHOD OF SYNTHESIS IS NOT REQUIRED

Circular 21 of 1994

Agar
Allantoin
Aloes
Aloin
Aluminium salts, (chloride, hydroxide and sulphate)
Ammonium salts (bicarbonate, bromide, chloride)
Balsam (Peru, Tolu)
Barium sulphate
Bentonite
Bismuth salts (carbonate, citrate, subnitrate)
Borax/boric acid
Brewers yeast
Calamine
Calcium salts (carbonate, hydroxide, sulphate)
Camphor
Carbon (activated)
Chalk
Copper salts (carbonate, sulphate)
Dextrose (glucose), fructose
Essential oils (almond, buchu, clove, eucalyptus, nutmeg)
Extracts concentrated (belladonna, cascara, ipec, scillae, valerian)
Ferric/ferrous salts (ammonium citrate, glycerophosphate, sulphate)
Gelatine
Gums (acacia, guar, resin, styrax, tragacanth, xanthan)
Honey
Ichthammol
Iodine
Kaolin
Lactose
Lanolin
Liquorice (various)
Magnesium salts (carbonate, chloride, hydroxide, oxide, sulphate, trisilicate)
Menthol
Oleo resins (capsicum, ginger, nutmeg)
Oils Natural (olive, coconut, cod-liver, evening primrose)
Pectins (apple citrus)
Petroleum jelly
Phenol
Potassium salts (bicarbonate, bromide, chloride, hydroxide, iodate, nitrate)
Pumice
Resins (jalap, podophyllin)
Resorcinol
Senna (leaves, pods)
Sodium salts of bromide, bicarbonate, chloride, citrate, fluoride, iodide, lactate
Sulphur
Strychnine
Tartaric acid
Tin salts
Waxes (beeswax, carnauba, paraffin, spermaceti)
Zinc salts

7 UPDATE HISTORY

Date	Reason for update	Version & publication
June 2016	New guideline to consolidate pharmaceutical and analytical and quality aspects of three guidelines and to include Annex: Stability	V1 June 2016
	Published for implementation	
June 2020	Addition of SAHPRA branding, naming and process and minor editing. Section 1: Guidance documents reference. 3.2.S.1.1: Reference to Annex B, inclusion of homeopathic medicines 3.2.S.2.2: Inclusion of homeopathic medicines 3.2.S.7: Inclusion of reference for stability for homeopathic medicines 3.2.P.5: Inclusion of reference for microbial limits for homeopathic medicines 3.2.P.8: Inclusion of reference for stability for homeopathic medicines Annex B: amendment of order of substance by quantity	V2 June 2020

ANNEX A

STABILITY TESTING

TABLE OF CONTENTS

PREAMBLE

The ICH Stability testing guideline, which has been developed within the Expert Working Group (Quality) of the International Conference on Harmonisation (ICH), provides a general indication of the requirements for stability testing. It primarily addresses the information required in applications for registration for new chemical entities and associated medicinal products. The ICH guideline latest additions/ updates appear on the ICH, FDA and EMA websites.

The Note for guidance on stability testing of existing active substances and related final products is in accordance with the ICH guideline with adaptations relevant for existing active substances and related final products including herbal substances and herbal preparations. This is available on the EMA website.

This guideline is adopted with only minor modifications. It contains aspects relating to testing conditions, numbers of batches to be tested and the requirements regarding follow-up stability data. Other relevant guidelines on the websites should also be referred to as required.

The World Health Organization Stability testing of active pharmaceutical ingredients and finished pharmaceutical products, Technical Report Series 953, Annex 2 guidelines make provision for the following long-term storage conditions for stability testing:

Climatic zone (CZ)	Definition	Criteria Mean annual temperature measured in the open air/ Mean annual partial water vapour pressure	Long-term Testing Conditions
I	Temperate climate	≤ 15 °C / ≤ 11 hPa	21 °C / 45 % RH
II	Subtropical & Mediterranean climate	> 15 to 22 °C / > 11 to 18 hPa	25 °C / 60 % RH
III	Hot and dry climate	> 22 °C / ≤ 15 hPa	30 °C / 35 % RH
IVA	Hot and humid climate	> 22 °C / > 15 to 27 hPa	30 °C / 65 % RH
IVB	Hot and very humid climate	> 22 °C / > 27 hPa	30 °C / 75 % RH

South Africa is classified in CZ II. In Table 2 of the WHO guideline the long-term stability conditions for WHO Member States by Region are listed, with South Africa indicated as zone IVA. Long-term stability studies conducted at zone IVA and IVB conditions, instead of or in addition to zone II will also be acceptable.

1 INTRODUCTION

1.1 Objectives of the Guideline

This guideline is applicable to chemical active substances and related finished products, herbal active substances, herbal active substance preparations and related herbal medicinal products and not to radiopharmaceuticals, biologicals and products derived by biotechnology.

The guideline seeks to exemplify the core stability data package required for such active substances and finished products, but leaves sufficient flexibility to encompass the variety of different practical situations that may be encountered due to specific scientific considerations and characteristics of the materials being evaluated. Alternative approaches can be used when there are scientifically justifiable reasons.

1.2 Scope of the Guideline

The guideline addresses the information to be submitted in registration applications for existing active substances and related finished products. For herbal active substances, herbal active substance preparations and herbal medicinal products, reference is made to the stability section of the Note for Guidance on Quality of Herbal Medicinal Products (EMEA/CPMP/2819/00). i.e.:

Since the herbal substance or herbal preparation in its entirety is regarded as the active substance, a mere determination of the stability of the constituents with known therapeutic activity will not suffice. The stability of other substances present in the herbal substance or in the herbal preparation, should, as far as possible, also be demonstrated, e.g., by means of appropriate fingerprint chromatograms. It should also be demonstrated that their proportional content remains comparable to the initial fingerprint.

If a herbal medicinal product contains combinations of several herbal substances or herbal preparations, and if it is not possible to determine the stability of each active substance, the stability of the medicinal product should be determined by appropriate fingerprint chromatograms, appropriate overall methods of assay and physical and sensory tests or other appropriate tests. The appropriateness of the tests must be justified.

In the case of a herbal medicinal product containing a herbal substance or herbal preparation with constituents of known therapeutic activity, the variation in content during the proposed shelf-life should not exceed +- 5 % of the declared assay value, unless justified. Broader limits may be acceptable. Nevertheless, no general limits can be recommended because the variation depends on the herbal substance used. Setting the limits is a case by case decision. In the case of a herbal medicinal product containing a herbal substance or herbal preparation where constituents with known therapeutic activity are unknown, a variation in marker content during the proposed shelf-life of +- 10 % of the initial assay value can be accepted if justified.

In the case of traditional herbal medicinal product for human use containing vitamins and/or minerals. The stability of the vitamins and/or minerals should be demonstrated as addressed below.

1.3 General Principles

The purpose of stability testing is to provide evidence on how the quality of an active substance or finished product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the active substance or a shelf-life for the finished product and recommended storage conditions.

2 ACTIVE SUBSTANCE

2.1 General Information

General information on the stability of the active substance is an integral part of the systematic approach to stability evaluation.

2.1.1 Active substances not described in an official pharmacopoeial monograph

Stability studies are required for active substances not described in a recognized official pharmacopoeial monograph.

2.1.2 Active substances described in an official pharmacopoeial monograph

For active substances described in an official pharmacopoeial monograph which covers the degradation products and for which suitable limits have been set but a re-test period is not defined, two options are acceptable:

a) It should be specified that the active substance complies with the pharmacopoeial monograph immediately prior to manufacture of the finished product. In this case no stability studies are required on condition that the suitability of the pharmacopoeial monograph has been demonstrated for the particular named source.

b) The re-test period should be based on the results of long term testing, taking the results of testing under accelerated or, where applicable, intermediate storage conditions, into consideration.

2.1.3 API monographs that do not include degradation products and limits thereof

When degradation products and suitable limits are not described in the accepted pharmacopoeia, it is acceptable to provide the relevant data published in the literature to support the proposed degradation pathways.

2.1.4 Herbal active substances and herbal active substance preparations

In the case of herbal medicinal products, active substances include herbal active substances and herbal active substance preparations. Herbal active substances which are used as starting material in the manufacturing process for a herbal active substance preparation shall comply with specification before use (e.g. before extraction).

2.2 Stress Testing Stress testing

Stress testing of the active substance 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.

2.2.1 Herbal active substances and herbal preparations

Stress tests are usually considered unnecessary for herbal active substances and herbal active substance preparations.

2.2.2 Active substances

For an active substance the following approaches may be used:

a) When an active substance is described in a recognized official pharmacopoeial monograph and fully meets its requirements no data are required on the degradation products if they are named under the headings “purity test” and / or “section on impurities”.

b) For active substances not described in an official pharmacopoeial monograph, there are two options: -

- When available, it is acceptable to provide the relevant data published in the literature to support the proposed degradation pathways.
- When no data are available in the scientific literature, including official pharmacopoeias, stress testing should be performed. Results from these studies will form an integral part of the information provided to regulatory authorities.

2.3 Selection of Batches

Two options are acceptable:

a) Stability information from accelerated and long term testing is to be provided on at least two production scale batches manufactured by the same manufacturing (synthetic) route and procedure described in part 3.2.S.2 of the application.

The long term testing and accelerated testing should cover a minimum of 6 months duration at the time of submission or

b) Stability information from accelerated and long term testing is to be provided on at least three pilot scale batches manufactured by the same manufacturing (synthetic) route and procedure described in part 3.2.S.2 of the application. The long term testing and accelerated testing should cover a minimum of 6 months duration at the time of submission.

2.4 Change in the manufacturing process of the active pharmaceutical ingredient

In case of amendment to the manufacturing process of the API, the following approaches may be considered as acceptable:

If the quality characteristics (e.g. physical characteristics, impurity profile) of the API are changed in such a way that stability may be compromised, comparative stability data are required in accelerated and long term testing conditions, on the API before and after the change:

- **for API known to be stable**: three months on one batch of at least pilot scale. An API is considered as stable if it is within the initial specifications when stored at 25 °C/ 60 % RH or 30 °C/65 % RH, respectively, (2 years) and 40 °C/75 %RH (3 months).
- **for API known to be unstable**: six and three months long term and accelerated respectively on two batches of at least pilot scale.

If the quality characteristics of the API are changed in such a way that it may impact the stability of the finished product, additional stability data on the finished product, in accelerated and long term testing conditions, three months on one batch of at least pilot scale, may be required.

2.5 Container Closure System

The stability studies should be conducted on the active substance packaged in a container closure system that is the same as or simulates the packaging proposed for storage and distribution.

2.6 Specification parameters to be tested *also refer sections 12 and 13.3 below*

The specification parameters to be included in stability studies should include those attributes of the active substance that are susceptible to change during storage and are likely to influence quality, safety and/or efficacy.

The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes. Validated stability-indicating analytical procedures should be applied.

Acceptance criteria are numerical limits, ranges and other criteria for the specific tests described and should include individual and total upper limits for impurities and degradation products.

The justification of individual and total upper limits for degradation products should be based on safety and/or efficacy considerations.

For active substances described in an official pharmacopoeial monograph the testing should be performed in accordance with the monograph or by using a test that has been cross-validated against the compendial test and the justification should be given that all potential impurities (process impurities and degradation products) from the actual manufacturing (synthetic) route are adequately controlled.

2.7 Testing Frequency

For long-term studies, frequency of testing should be sufficient to establish the stability profile of the active substance. The frequency of testing at the long term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed re-test period.

2.7 Testing Frequency - continued

At the accelerated storage condition, a minimum of three points, including the initial and final time points (e.g. 0, 3, and 6 months), from a 6-month study is recommended. Where an expectation (based on development experience) exists that results from accelerated studies are likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design.

When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g., 0, 6, 9, 12 months), from a 12-month study is recommended.

For herbal drugs and herbal drug preparations on which the applicant in the possession of historical batch data, the testing frequency may be reduced if justified by the applicant.

2.7 Storage Conditions

2.7.1 General storage conditions

In general, an active substance should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

The long term testing for both options a) and b) (section 2.3 above) should cover a minimum of 6 months' duration at the time of submission and should be continued for a period of time sufficient to cover the proposed re-test period. Additional data accumulated during the assessment period of the registration application should be submitted to the authorities if requested.

Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

Long term, accelerated, and, where appropriate, intermediate storage conditions for active substances are detailed in the sections below. The general case applies if a subsequent section does not specifically cover the active substance. Alternative storage conditions can be used if justified.

	Storage conditions	Minimum time period at submission
Long-term*	25 ± 2 °C / 60 ± 5 % RH or 30 ± 2 °C / 65 ± 5 % RH	6 months (option a and b)
Intermediate	30 ± 2 °C / 65 ± 5 % RH	6 months*****
Accelerated	40 ± 2 °C / 75 ± 5 % RH	3 months

*****If long term stability studies are performed at 30 °C ± 2 °C/65 % RH ± 5 % RH, no additional data under intermediate conditions is required.

Stability data over the full shelf-life period should be submitted for confirmation of the provisional retest period.

For herbal drugs and herbal drug preparations, testing at the accelerated storage condition or at the intermediate storage condition may be omitted if clearly justified and if the storage conditions at or below 25 °C are clearly labelled on the product.

When "significant change" occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. Testing at the intermediate storage condition should include all tests, unless otherwise justified.

The initial application should include a minimum of 6 months' data from a 12-months study at the intermediate storage condition. "Significant change" for an active substance is defined as failure to meet its specification.

2.7.2 Active substances intended for storage in a refrigerator

	Storage conditions	Minimum time period at submission
Long-term	5 ± 3 °C	6 months (option a and b)
Intermediate	30 ± 2 °C / 65 ± 5 % RH	6 months
Accelerated	25 ± 2 °C / 60 ± 5 % RH	6 months

Data from refrigerated storage should be assessed according to the evaluation section of this guideline, except where explicitly noted below.

If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed re-test period should be based on the real time data available at the long term storage condition.

If significant change occurs within the first 3 months' testing at the accelerated storage condition, a discussion should be provided to address the effect of short term excursions outside the label storage condition, e.g., during shipping or handling. This discussion can be supported, if appropriate, by further testing on a single batch of the active substance for a period shorter than 3 months but with more frequent testing than usual.

It is considered unnecessary to continue to test an active substance through 6 months when a significant change has occurred within the first 3 months.

2.7.3 Active substances intended for storage in a freezer

	Storage conditions	Minimum time period at submission
Long-term	-20 ± 5 °C	6 months (option a and b)
Intermediate	30 ± 2 °C / 65 ± 5 % RH	6 months
Accelerated	40 ± 2 °C / 75 ± 5 % RH	3 months

For active substances intended for storage in a freezer, the re-test period should be based on the real time data obtained at the long-term storage condition.

In the absence of an accelerated storage condition for active substances intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g., 5 °C ± 3 °C or 25 °C ± 2 °C) for an appropriate time period should be conducted. Such a study will address the effect of short term excursions outside the proposed label storage condition, e.g., during shipping or handling.

2.7.4 Active substances intended for storage below –20 °C

Active substances intended for storage below –20 °C should be treated on a case-by-case basis.

2.8 Stability Commitment

When available long term stability data on primary batches do not cover the proposed re-test period granted at the time of approval, a commitment should be made to continue the stability studies post approval in order to firmly establish the re-test period.

Where the submission includes long-term stability data on three production batches covering the proposed re-test period, a post approval commitment is considered unnecessary.

Otherwise one of the following commitments should be made:

1 If the submission includes data from stability studies on at least three production batches, a commitment should be made to continue these studies through the proposed re-test period.

2 If the submission includes data from stability studies on fewer than three production batches, a commitment should be made to continue these studies through the proposed re-test period and to place additional production batches, to a total of at least three, on long term stability studies through the proposed re-test period.

3 If the submission does not include stability data on production batches, a commitment should be made to place the first three production batches on long term stability studies through the proposed re-test period. The stability protocol used for long-term studies for the stability commitment should be the same as that for the primary batches, unless otherwise scientifically justified.

2.9 Evaluation

An active substance is considered as stable if it is within the defined/regulatory specifications when stored for at least 2 years at 25 °C/60 % RH or at the alternative storage condition 30 °C/65 % RH and for at least 6 months at 40 °C/75 % RH.

Refer to Evaluation under Finished Product, section 3.9 below.

2.10 Statements/Labelling

The storage temperature should be based on the stability evaluation of the active substance.
The use of terms such as “ambient conditions” or “room temperature” is unacceptable.

3 FINISHED PRODUCT

3.1 General

The design of the formal stability studies for the finished product should be based on knowledge of the behaviour and properties of the active substance and the dosage form.

3.2 Photostability Testing

Photostability testing of *new* active substances and medicinal products/complementary medicines should be conducted on at least one primary batch of the final product if appropriate. *(Stress tests are usually considered unnecessary for herbal active substances and herbal active substance preparations – refer 2.2.1 above.)*

Refer to the Note for Guidance on Photostability Testing of New Active Substances and Medicinal Products (CPMP/ICH/279/95).

3.3 Selection of Batches

At the time of submission data from stability studies should be provided for batches of the same formulation and dosage form with API from the API manufacturers being applied for (in Module 3.2.S) in the container closure system proposed for marketing. Two options are acceptable:

a) For conventional dosage forms (e.g. immediate release solid dosage forms, solutions) and when the active substances are known to be stable, stability data on at least two pilot scale batches are acceptable.

b) For critical dosage forms or when the active substances are known to be unstable, stability data on three primary batches are to be provided. Two of the three batches should be of at least pilot scale, the third batch may be smaller. The manufacturing process used for primary batches should simulate that to be applied to production batches and should provide product of the same

quality and meeting the same specification as that intended for marketing. Where possible, batches of the finished product should be manufactured by using different batches of the active substance.

Stability studies should be performed on each individual strength and container size of the finished product unless bracketing or matrixing is applied. Other supporting data can be provided.

Data on laboratory scale is not acceptable as primary stability information. Data on associated formulations or packaging may be submitted as supporting information provided that the difference in formulation is clearly stated.

The first two production batches manufactured post-approval, if not submitted in the original application for registration, should be placed on long-term stability using the same stability protocols as in the approved application for registration.

The long-term testing should cover at least six or nine months (option a or b respectively) duration at the time of submission. The manufacturing process to be used should meaningfully simulate that which would be applied to large-scale batches for marketing. The process should provide product of the same quality intended for marketing, and meet the same quality specification that are to be applied to release of material.

3.4 Container Closure System

Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing (including, as appropriate, any secondary packaging and container label).

Any available studies carried out on the product outside its immediate container or in other packaging materials can form a useful part of the stress testing of the dosage form or can be considered as supporting information, respectively.

Where package container sealant integrity is to be assessed, higher than 75 % relative humidity may be appropriate to stress its adhesive properties at 30 to 40 °C e.g. blister units and strip packages. Alternatively, sealant integrity can be performed through physical testing of the pack itself.

The loss of moisture can be important for liquid formulations, semisolid and certain solid dosage forms packed in moisture permeable containers. Studies at low relative humidity and high temperature, for a limited period of time, may be appropriate for these products.

For most dosage forms, stability data need only be obtained for the container closure system to be marketed, provided that all container closure systems are of identical composition and seal integrity. A brief justification for the container size chosen, e.g. larger air volume, or largest surface contact, etc. should also be included. If the product is to be marketed in more than one type of container, and the resistance to variables such as moisture permeation, oxygen permeation, light diffusion, etc. are demonstrated to be equal to, or better than, existing container closure systems, additional stability testing would usually not be required for solid dosage forms in the more protective packaging.

In instances where solid oral dosage forms will be marketed packaged in a “moisture permeable” material (e.g. polyethylene, polypropylene, polyvinyl chloride, etc.), the stability of the product should be determined under conditions of high humidity and elevated temperature.

Stability may be conducted in the least protective container closure system if the superiority of the other containers can be proven. These data should be included in the CTD Section 3.2.P.8.

The time that the product is stored in the bulk container, prior to packing into the final immediate container, constitutes part of the approved shelf-life; that is, the date of expiry remains a function of the date of manufacture, not the date of packaging. Stability data should be submitted for bulk products

that are stored for a period of time prior to packaging into the final immediate containers, i.e. for 25 % or more of the approved shelf-life.

3.5 Specification parameters to be tested

Stability studies should include testing of those attributes of the finished product that are susceptible to change during storage and are likely to influence quality, safety and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes, preservative content (e.g. antioxidant, antimicrobial preservative), and functionality tests (e.g., for a dose delivery system).

Analytical procedures should be fully validated and stability indicating. Whether and to what extent replication should be performed will depend on the results of validation studies.

Shelf life acceptance criteria should be derived from consideration of all available stability information. It may be appropriate to have justifiable differences between the shelf life and release acceptance criteria based on the stability evaluation and the changes observed on storage.

Any differences between the release and shelf life acceptance criteria for antimicrobial preservative content should be supported by a validated correlation of chemical content and preservative effectiveness demonstrated during drug development on the product in its final formulation (except for preservative concentration) intended for marketing.

A single primary stability batch of the finished product should be tested for antimicrobial preservative effectiveness (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.

3.6 Testing Frequency

For long-term studies, frequency of testing should be sufficient to establish the stability profile of the finished product. The frequency of testing at the long term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed shelf life.

At the accelerated storage condition, a minimum of three points, including the initial and final time points (e.g. 0, 3, and 6 months), from a 6-month study is recommended. Where an expectation (based on development experience) exists that results from accelerated testing are likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design.

When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g. 0, 6, 9, 12 months), from a 12-month study is recommended.

For herbal medicinal products on which the applicant in the possession of historical batch data, the testing frequency may be reduced if justified.

Reduced designs i.e. matrixing or bracketing, where the testing frequency is reduced or certain factor combinations are not tested at all, can be applied, if justified.

3.7 Storage Conditions

In general, a finished product should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

	Storage conditions	*Minimum time period at submission
Long-term**	25 ± 2 °C / 60 % ± 5 % RH or 30 ± 2 °C/65 % ± 5 % RH or 30 ± 2 °C/75 % ± 5 % RH	6 months (option a) 9 months (option b)
Intermediate	30 ± 2 °C/ 65 % ± 5 % RH	6 months if significant change at accelerated
Accelerated	40 ± 2 °C / 75 % ± 5 % RH	3 months

*However, all the stability data that should reasonably be available at the time of submission should be submitted. At the time of responding to a Pharmaceutical and Analytical Committee recommendation, any available further/follow-up stability data may/should be submitted provided that the stability data previously submitted is also included, i.e. a complete data set of Module 3.2.P.8 with the additional data excluding unchanged analytical methods and analytical method validation. Refer to 6.4 below.

**If the long-term condition is 30 °C ± 2 °C/65 % RH ± 5 % RH (or 30 °C ± 2 °C/75 % RH ± 5 % RH) there is no intermediate condition.

Stability testing of the finished product after constitution or dilution, if applicable, should be conducted to provide information for the labelling on the preparation, storage condition, and in-use period of the constituted or diluted product. This testing should be performed on the constituted or diluted product through the proposed in-use period on primary batches as part of the formal stability studies at initial and final time points and, if full shelf life long term data will not be available before submission, at six months or the last time point for which data will be available. In general, this testing need not be repeated on commitment batches.

Long-term studies should be continued for a period of time sufficient to cover the proposed shelf life.

Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

Heat-sensitive FPPs should be stored under an alternative lower temperature, which will eventually become the designated long-term storage temperature. Where a lower temperature is used, the 3 months accelerated testing should be carried out at a temperature at least 15 °C above its designated long-term storage temperature (together with appropriate relative humidity conditions for that temperature).

Significant change

When a “significant change" occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. The initial application should include a minimum of 6 months’ data from a 12-month study at the intermediate storage condition. In general, “significant change” for a finished product is defined as:

1 A 5 % change in assay from its initial value; or failure to meet the acceptance criteria for potency when using biological or immunological procedures;
2 Any degradation product exceeding its acceptance criterion;
3 Failure to meet the acceptance criteria for appearance, physical attributes, and functionality test (e.g. colour, phase separation, resuspendability, caking, hardness, dose delivery per actuation); however, some changes in physical attributes (e.g., softening of suppositories, melting of creams, partial loss of adhesion for transdermal products) may be expected under accelerated conditions; And, as appropriate for the dosage form:
4 Failure to meet the acceptance criterion for pH; or
5 Failure to meet the acceptance criteria for dissolution for 12 dosage units.

3.7.1 Finished products packaged in impermeable containers

Sensitivity to moisture or potential for solvent loss is not a concern for finished products packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus, stability studies for products stored in impermeable containers can be conducted under any controlled or ambient humidity condition.

3.7.2 Finished products packaged in semi-permeable containers

Aqueous-based products packaged in semi-permeable containers should be evaluated for potential water loss in addition to physical, chemical, biological, and microbiological stability. This evaluation can be carried out under conditions of low relative humidity, as discussed below. Ultimately, it should be demonstrated that aqueous-based finished products stored in semi-permeable containers could withstand low relative humidity environments. Other comparable approaches can be developed and reported for non-aqueous, solvent-based products.

	Storage conditions	*Minimum time period at submission
Long-term**	25 ± 2 °C / 40 ± 5 % RH or 30 ± 2 °C / 35 ± 5 % RH	6 months (option a), 9 months (option b)
Intermediate	30 ± 2 °C / 65 ± 5 % RH	6 months*
Accelerated	40 ± 2 °C / nmt 25 ± 5 % RH	6 months

When a significant change other than water loss occurs during the 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be performed as described under the general case to evaluate the temperature effect at 30 °C.

A significant change in water loss alone at the accelerated storage condition does not necessitate testing at the intermediate storage condition. However, data should be provided to demonstrate that the finished product will not have significant water loss throughout the proposed shelf life if stored at 25 °C and the reference relative humidity of 40 % RH.

A 5 % loss in water from its initial value is considered a significant change for a product packaged in a semi-permeable container after an equivalent of 3 months' storage at 40 °C/NMT 25 % RH. However, for small containers (1 ml or less) or unit-dose products, a water loss of 5 % or more after an equivalent of 3 months' storage at 40 °C/nmt 25 % RH may be appropriate, if justified.

An alternative approach to studying at the reference relative humidity as recommended in the table above (for either long term or accelerated testing) is performing the stability studies under higher relative humidity and deriving the water loss at the reference relative humidity through calculation. This can be achieved by experimentally determining the permeation coefficient for the container closure system or, using the calculated ratio of water loss rates between the two humidity conditions at the same temperature. The permeation coefficient for a container closure system can be experimentally determined by using the worst case scenario (e.g. the most diluted of a series of concentrations) for the proposed finished product.

For an example of an approach for determining water loss: refer to CPMP/QWP/122/02 section 2.2.7.3.

3.7.3 Finished products intended for storage in a refrigerator

	Storage conditions	*Minimum time period at submission
Long-term	5 ± 3 °C	6 months (option a), 9 months (option b)
Accelerated	25 ± 2 °C / 5 ± 5 % RH	6 months

If the finished product is packaged in a semi-permeable container, appropriate information should be provided to assess the extent of water loss. Data from refrigerated storage should be assessed according to the evaluation section of this guideline, except where explicitly noted below.

If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed shelf life should be based on the real time data available from the long-term storage condition. If significant change occurs within the first 3 months' testing at the accelerated storage condition, a discussion should be provided to address the effect of short term excursions outside the label storage condition, e.g., during shipment and handling.

This discussion can be supported, if appropriate, by further testing on a single batch of the finished product for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a product through 6 months when a significant change has occurred within the first 3 months.

3.7.4 Finished products intended for storage in a freezer

	Storage conditions	*Minimum time period at submission
Long-term	-20 ± 5 °C	6 months (option a), 9 months (option b)
Accelerated	40 ± 2 °C / 75 ± 5 % RH	3 months

For finished products intended for storage in a freezer, the shelf life should be based on the real time data obtained at the long-term storage condition. In the absence of an accelerated storage condition for finished products intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g., 5 °C ± 3 °C or 25 °C ± 2 °C) for an appropriate time period should be conducted to address the effect of short term excursions outside the proposed label storage condition.

3.7.5 Finished products intended for storage below -20 °C

Finished products intended for storage below –20 °C should be treated on a case-by-case basis.

3.8 Stability Commitment

When available long-term stability data on primary batches do not cover the proposed shelf life granted at the time of approval, a commitment should be made to continue the stability studies post approval in order to firmly establish the shelf life.

Where the submission includes long-term stability data on three production batches covering the proposed shelf life, a post approval commitment is considered unnecessary. Otherwise, one of the following commitments should be made:

1 If the submission includes data from stability studies on at least three production batches, a commitment should be made to continue the long-term studies through the proposed shelf life.

2 If the submission includes data from stability studies on fewer than three production batches, a commitment should be made to continue the long term studies through the proposed shelf life, and to place additional production batches, to a total of at least three, on long term stability studies through the proposed shelf life and on accelerated studies for 6 months.

3 If the submission does not include stability data on production batches, a commitment should be made to place the first three production batches on long term stability studies through the proposed shelf life and on accelerated studies for 6 months. The stability protocol used for studies on commitment batches should be the same as that for the primary batches, unless otherwise scientifically justified.
Where intermediate testing is called for by a significant change at the accelerated storage condition for the primary batches, testing on the commitment batches can be conducted at either

the intermediate or the accelerated storage condition. However, if significant change occurs at the accelerated storage condition on the commitment batches, testing at the intermediate storage condition should also be conducted.

3.9 Evaluation

A systematic approach should be adopted in the presentation and evaluation of the stability information, which should include, as appropriate, results from the physical, chemical, biological and microbiological tests, including particular attributes of the dosage form (for example, dissolution rate for solid oral dosage forms).

Any evaluation should consider not only the assay, but also the degradation products and other appropriate attributes. Where appropriate, attention should be paid to reviewing the adequacy of the mass balance and different stability and degradation performance.

The purpose of the stability study is to establish, based on testing a minimum of two or three batches of the finished product, a shelf life and label storage instructions applicable to all future batches of the finished product manufactured and packaged under similar circumstances/conditions.

The degree of variability of individual batches affects the likelihood of a future production batch remaining within specification until the expiration date.

Where the data show so little degradation and so little variability that it is apparent from looking at the data that the requested shelf life will be granted, it is normally unnecessary to go through the formal statistical analysis; providing a justification for the omission should be sufficient.

An approach for analysing data on a quantitative attribute that is expected to change with time is to determine the time at which the 95 one-sided confidence limit for the mean curve intersects the acceptance limit. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g. p values for level of significance of rejection of more than 0,25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall shelf life should be based on the minimum time a batch can be expected to remain within accepted and justified limits.

The nature of any degradation relationship will determine whether the data should be transformed for linear regression analysis. Usually the relationship can be represented by a linear, quadratic, or cubic function on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit of the data on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

Limited extrapolation of the real time data from the long-term storage condition beyond the observed range to extend the shelf life may be done (refer section 5 below), if justified. This justification should be based on what is known about the mechanisms of degradation, the results of testing under accelerated conditions, the goodness of fit of any mathematical model, batch size, existence of supporting stability data, etc. However, this extrapolation assumes that the same degradation relationship will continue to apply beyond the observed data.

If real time data are supported by results from studies conducted under accelerated or intermediate storage conditions, the re-test period/shelf life may be extended beyond the end of real time studies.

The extrapolated retest period or shelf-life may be up to twice, but should not be more than 12 months beyond, the period covered by real time data, depending on the change over time, variability of data observed, proposed storage conditions and extent of statistical analyses performed. (*refer section 5 below*).

3.10 Statements/Labelling

The storage temperature should be based on the stability evaluation of the FPP.

The use of terms such as “ambient conditions” or “room temperature” is unacceptable. The storage temperature must be specified as e.g. “ at or below 25 °C”.

There should be a direct link between the label statement and the demonstrated stability characteristics of the FPP.

4 PRESENTATION OF STABILITY DATA

4.1 The criteria for acceptance of each parameter (minimum and maximum values), relating to stability, should be stated.

4.2 Overages in the formulation of batches, included in the stability investigation, should be clearly stated.

4.3 The actual analytical results obtained at the commencement (zero time) and at nominated time intervals throughout the trial (for example 0, 3, 6, 9, 12, 18, 24, 30, 36 months, which can if necessary, be adapted to suit the product) should be provided in a tabulated form. For products predicted to degrade rapidly, more frequent sampling is necessary.

4.4 The container closure system used should be clearly indicated, e.g. the type, nature, grade and colour of the material of the container and closure should be stated. The composition of strip packaging, blister packaging and liners, and size of the container(s) or pack-size, should also be clearly stated.

4.5 Storage conditions should be clearly defined in respect of the temperature, light, humidity, opening and closing of container, whether stored upright or inverted, whether a desiccant is included in the container and the inclusion of foam/cotton wool.

4.6 The name and strength of the product, dosage form, batch size, batch number, name of final product manufacturer, manufacturer of API, dates of final product manufacture and initial testing, should be stated.

4.7 The actual result obtained for an assay at the beginning of the stability trial should be recorded and compared with subsequent values.

4.8 Assay results should be expressed as a percentage of the label claim. Assay results for subsequent checkpoints should be given in the same way, as a percentage.

4.9 Quantitative results should be reflected wherever relevant, in which case, the expression “complies” will not suffice.

4.10 All results obtained should be discussed and conclusions drawn from the stability studies should be stated. A shelf-life should be extrapolated or derived from the results. Explanations should be given where necessary, e.g. for anomalous or unusual results, change in assay method. Results should be processed utilising current statistical methods and any assumption made should be statistically tested at the 90 to 95 % confidence level.

4.11 A stability-indicating method refers to a specific analytical method and does not absolve the applicant from submitting reasons why the assay methods used are assumed to be stability-indicating.

4.12 An assurance that long-term testing will continue to cover the shelf-life period should be given in Section 3.2.P.8 (a written undertaking at the time of submission of the application) in accordance with sections 2.8 and 3.8 above.

In accordance with the recommendation under “Testing frequency” products should be tested at least annually after the second year.

4.13 The stability data should be presented in tabulated format, e.g.:

Product Name: Batch No.: Batch Size: Date of Manufacture:		Packaging (material and pack sizes): Storage conditions: Name of manufacturer: Manufacturer of API:					
Date of commencement of stability study:		**Time intervals (months)**					
Title of Specification	Limits	0	3	6	9	12	24

5 PREDICTION OF SHELF-LIFE

At least nine months' data, derived from the product stored at the maximum recommended storage conditions, and three months under accelerated/stress conditions for generic products is required for consideration of a provisional shelf-life of 24 months.

Generally a provisional shelf-life shall only be assigned provided that the stability investigation of the product, as above, has been satisfactorily completed.

5.1 APIs and FPPs intended for room temperature storage

5.1.1 Long-term and accelerated show little or no change and little or no variability
Extrapolation of the retest period or shelf life up to twice, but not more than 12 months beyond the period covered by long-term data, can be proposed.

5.1.2 Long-term or accelerated data show change over time and/or variability
Extrapolation of the retest period or shelf life up to one and a half times, but not more than 6 months beyond the period covered by long-term data, can be proposed.

For data amenable to statistical analysis and supported by statistical analysis and relevant supporting data, extrapolation of the retest period or shelf life up to twice but not more than 12 months beyond the period covered by long-term data, can be proposed.

5.2 APIs and FPPs intended for storage in a refrigerator

5.2.1 Long-term and accelerated data show no or little change and no or little variability.
Extrapolation of the retest period or shelf life up to one and a half times, but not more than 6 months beyond the period covered by long-term data, can be proposed.

5.2.2 Accelerated data show significant change between 3 and 6 month's testing at accelerated conditions.
If significant change occurs between 3 and 6 months testing at the accelerated condition, the proposed retest period should be based on the long term data, extrapolation is not considered appropriate.

5.3 APIs and FPPS intended for storage in a freezer

The retest period or shelf life should be based on long term data.

5.4 Extrapolated retest period or shelf-life

Applicants are reminded that a provisional retest period or shelf-life allocated on the basis of extrapolation is granted on condition that the applicant has undertaken to continue and complete the required studies and to submit the results as they become available. Care should be taken to include in

the protocol for commitment batches, a time point that corresponds to the end of the extrapolate retest period or shelf life.

6 FOLLOW-UP STABILITY DATA

6.1 The provisional shelf-life should be confirmed by stability data, derived from at least two production batches, stored at the maximum recommended storage conditions for the full duration of the shelf-life.

6.2 For products containing option b) active substances, the provisional shelf-life should be confirmed by stability data derived from at least three production batches.

6.3 Stability trials, involving the product stored at the maximum recommended temperature, should be continued for the full period to confirm the provisional shelf-life.

6.4 The application should include all the stability data in support of the shelf-life extension (including previously submitted data for the relevant batches), i.e. a complete data set of Module 3.2.P.8 with the additional data excluding unchanged analytical methods and analytical method validation. Reference alone to data submitted previously, is not acceptable.

7 CALCULATION OF EXPIRY DATE

The expiry date is calculated from the date of manufacture. If the production batch contains reprocessed material, the expiry date is calculated from the date of manufacture of the oldest reprocessed batch. It should also be verified that the batch will meet the final product specification for the full period of the allocated shelf-life.

The date of production of a batch is defined as the date that the first step is performed involving combining the API(s) with other IPIs. For medicinal products consisting of a single API filled into a container, the initial date of the filling operation is taken as the date of production.

8 STORAGE IN BULK

The suitability of the container used for in-process storage and transportation of bulk product in terms of compatibility, moisture permeation and closure seal ability must be considered/addressed.

9 EXTENSION OF SHELF-LIFE (Refer to the Amendments guideline)

The shelf-life may not be extended until the data have been evaluated and approved. The application should include all the stability data in support of the shelf-life extension (including previously submitted data for the relevant batches). Reference alone to data, submitted previously, is not acceptable.

10 AMENDMENTS

Procedures for submission of data relating to changes in formulation, site and method of manufacture and packaging, which may influence the shelf-life quality of a product, are outlined in the Amendments guideline.

11 GLOSSARY

The following terms, which have been in general use, and their definitions, are provided to facilitate interpretation of the guideline.

Accelerated testing

Studies designed to increase the rate of chemical degradation or physical change of an API or product by using exaggerated storage conditions as part of the formal, definitive, storage programme. These

data, in addition to long-term stability studies, may also be used to assess longer term chemical effects at non-accelerated conditions and to evaluate the impact of short-term excursions outside the label storage conditions, such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes that may occur.

Active Pharmaceutical Ingredient (API)/ Active substance / Drug Substance/Medicinal Substance

A substance or compound that is intended to be used in the manufacture of a pharmaceutical product / complementary medicine (generally with inactive pharmaceutical ingredients) as a pharmacologically active ingredient that is responsible for its physiological or pharmacological action which may include a whole substance such as a single herb.

Bracketing

The design of a stability schedule so that at any time point, only the samples at the extremes, for example of container size and/or dosage strengths, are tested. The design assumes that those at the extremes represent the stability of the intermediate samples. Where a range of dosage strengths are to be tested, bracketing designs are particularly applicable if the strengths are very closely related in composition. Examples include a tablet range made with different compression masses of a similar basic granulation, or a capsule range made by filling different plug fill masses of the same basic composition into different size capsule shells.

Where a range of sizes of immediate containers is to be evaluated, bracketing designs may be applicable if the composition of the material from which the containers are made, and the type of closure, are the same throughout the range.

Climatic Zones

This refers to the concept of dividing the world into four zones based on the prevalent annual climatic conditions. South Africa is classified in CZII (Subtropical & Mediterranean climate) to take into account the climate in South Africa that would most affect the storage of pharmaceuticals/medicines. The South African Weather Service Climatic classification of South Africa ranges from “Desert (arid)” in the west to “All-year rain with hot summers” in the eastern coastal region. Zone IV conditions are regarded as a global zone of highest stringency.

Dosage Form/Preparation

A pharmaceutical product type, for example tablet, capsule, solution, cream, etc. that contains an API generally but not necessarily, in association with inactive pharmaceutical ingredients.

Excipient/Inactive pharmaceutical ingredient (IPI)

Anything other than the API in the dosage form.

Expiry / Expiration Date

The date placed on the container/label of a product designating the time during which a batch of the product is expected to remain within the approved shelf-life specification, if stored under defined conditions and after which it should not be used.

Finished Pharmaceutical Product (FPP)

The dosage form in the final immediate packaging intended for marketing.

Formal (Systematic) Studies

Formal studies are those undertaken according to a pre-approval stability protocol and which embraces the principles of these guidelines.

Impurity - *in Quality guideline*

Long-Term (Real-Time) Testing

This refers to the stability evaluation of the physical, chemical, biological, and microbiological characteristics of a product and its API, which covers the expected duration of the shelf-life, and retest period, that are claimed in the application for registration, and which will appear on the label.

Markers

Markers are chemically defined constituents or groups of constituents of a herbal substance, a herbal preparation or a herbal medicinal product which are of interest for control purposes independent of whether they have any therapeutic activity. Markers serve to calculate the quantity of herbal substance(s) or herbal preparation(s) in the herbal medicinal product if the marker has been quantitatively determined in the herbal substance or herbal preparation.

There are two categories of markers:
Active markers are constituents or groups of constituents which are generally accepted to contribute to the therapeutic activity.
Analytical markers are constituents or groups of constituents that serve for analytical purposes.

Mass Balance/Material Balance

The process of adding together the assay value, and levels of degradation products, to see how closely these add up to a 100 per cent of the initial value, with due consideration to the level of analytical precision. This concept is a useful scientific guide for evaluating data, but is not achievable in all circumstances. The focus may instead be on assuring the specificity of the assay, the completeness of the investigation of routes of degradation, and the use, if necessary, of identified degradants as indicators of the extent of degradation via particular mechanisms.

Matrixing

The statistical design of a stability schedule such that only a fraction of the total number of samples is tested at any specific sampling point. At a subsequent sampling point, different sets of samples of the total number, would again be tested. The design assumes that the stability of the samples tested represents the stability of all samples.

The differences in the samples for the same product should be identified as, for example, covering different batches, different strengths, different sizes of the same container and closure, and possibly in some cases, different container/closure systems.

Matrixing permits reduced testing when more than one variable is being evaluated. Thus the design of the matrix will be dictated by the factors that need to be covered and evaluated. The potential complexity precludes inclusion of specific details and examples here. It will, however, be prudent to discuss the design in advance with Authority, where possible. It is essential that, in each case, all batches are tested initially, and at the end, of the long-term testing programme.

Mean Kinetic Temperature

When establishing the mean value of the temperature, the formula of Haynes (1971)* can be used to calculate the mean kinetic temperature. It is higher than the arithmetic mean temperature and takes into account the Arrhenius equation from which Haynes derived his formula.
*Haynes, J.D. Pharm. Sci. J, 60, 927-929, 1971.

New Chemical Entity/New Molecular Entity/New API

A substance, which has not previously been registered as a new API, with the Authority.

Pilot Plant Scale

The manufacture of either API, or product, by a procedure fully representative of, and simulating that to be used on, a full manufacturing scale. For oral solid dosage forms, this is generally taken to be at a minimum scale of one-tenth that of full production batch, or a 100 000 tablets or capsules, whichever is greater.

Primary Stability Data
These are data on the API stored in the proposed packaging under storage conditions that support the proposed retest date. It also refers to data on the product stored in the proposed container-closure system for marketing under storage conditions that support the proposed shelf-life.

Provisional Shelf-life
A provisional shelf-life determined by projecting results from less than full term data (such as "accelerated studies") and storage under maximum recommended conditions for a period motivated by the applicant using the dosage form to be marketed in the proposed container-closure system.

Release Specification - *in Quality guideline*

Retest Date
The date when samples of the API should be re-examined to ensure that material is still suitable for use.

Retest Period
The period of time during which the API can be considered to remain within the specifications and, therefore, acceptable for use in the manufacture of a given FPP, provided that it has been stored under the defined conditions. After this period, the batch should be re-tested for compliance to its specifications and then used immediately.

Shelf-life/Expiration Dating Period
The time interval that a product is expected to remain within the approved shelf-life specifications, provided that it is stored under the conditions defined on the label in the proposed container and closure system.

The shelf-life is used to establish the expiry date of individual batches. It is the length of time required for:

the least stable API to degrade to the specified, motivated and approved or proposed, fraction of the labelled quantity,
some element of pharmaceutical elegance to drop to an unacceptable level, or
an arbitrary minimum of two years, unless otherwise determined by Authority.

The shelf-life could also reflect the length of time required for:

a measurable increase in toxicity, as shown by either animal experiments or clinical adverse reaction reports, or
a measurable loss in reported clinical effectiveness(even though analytical methods show little or no reduction in apparent concentration).

Shelf-Life Specification - *in Quality guideline*

Stability-Indicating Assay Methodology
Analytical method(s) that will quantitatively differentiate between the API and all known degradation products and/or related impurities.

Stability
The capacity of an API or dosage form to remain within specifications established to assure its identity, purity, strength and critical physico-chemical characteristics.

Storage Conditions
An acceptable variation in temperature and relative humidity of storage facilities. The equipment should be capable of controlling temperature to a range of ± 2 ^{o}C and Relative Humidity to ± 5 % RH. The real temperatures and humidities should be monitored during stability storage. Short-term spikes due to opening of doors of the storage facility are accepted as unavoidable. The effect of variations during equipment failure should be addressed by the applicant and reported, if judged to impact stability results.

Exceptions that exceed these ranges (i.e. greater than 2 ºC and/or 5 % RH) for more than 24 hours, should be described in the study report and their impact assessed.

Strength

A quantitative measure of API, as well as other ingredients, requiring quantification.

Stress Testing (Active Pharmaceutical Ingredient API) ***not usually required for herbals***

These studies are undertaken to elucidate intrinsic stability characteristics of the API. Such testing is part of the development strategy, which is normally carried out under more severe conditions than those used for accelerated tests. Stress testing is conducted to provide data on breakdown products and decomposition mechanisms for the API.

The severe conditions that may be encountered during distribution can be covered by stress testing of definitive batches of the API. These studies should establish the inherent stability characteristics of the molecule, such as the degradation pathways, and lead to identification of degradation products and, hence, support the suitability of the proposed analytical procedures. The extensiveness of the studies will depend on the individual API and type of FPP.

This testing is likely to be carried out on a single batch of material and will include the effect of temperature, in 10 °C increments above the accelerated temperature test condition (e.g. 50 oC, 60 oC, etc.), humidity where appropriate (e.g. 75 % or greater), oxidation and photolysis on the API, plus its susceptibility to hydrolysis across a wide range of pH values when in solution and suspension. Results from these studies will form an integral part of the information provided to the Authority.

Photostability testing should be an integral part of stress testing.

It is recognised that some degradation pathways can be complex and that under forced conditions, decomposition products may be observed which are unlikely to be formed under accelerated or long-term testing conditions. Information on such degradation products may be useful in developing and validating suitable analytical methods. However, it may not always be necessary to test for such compounds, particularly if it has been demonstrated that in practice, these are not formed.

Stress Testing (FPP)

Studies undertaken to assess the effect of severe conditions on a product. Light testing should be an integral part of stress testing (see above).

Special test conditions for specific products (e.g. metered dose inhalations, creams and emulsions) may require additional stress studies.

Supporting Stability Data

These include data other than primary stability data, such as stability data on early batches of API using a different route of synthesis, small scale batches of materials, investigational formulations not proposed for marketing, related formulations, product presented in containers and/or closure systems other than those proposed for marketing, information regarding test results on containers, and other scientific rationale that support the analytical procedures, the proposed retest period, or shelf-life and storage conditions.

12 APPROPRIATE TESTS

Both physical and chemical characteristics of the product should be monitored during storage. The possibility of interaction between the components of a fixed-combination product should be considered. Where a pharmaceutical interaction appears possible, the applicant should submit data to show that it either does not occur, or that it is clearly recognised and defined. Where significant interaction with the packaging is likely, the effects on the product and on the packaging (e.g. due to leaching of extractables,

or due to absorption of constituents), should be evaluated and the results reported. The following tests should always be included for all dosage forms:

- Appearance
- Assay of all actives or suitable pharmaceutical or therapeutic markers
- Degradation, if relevant

Assay

Detailed records of all analytical methods used in the stability studies should be kept along with validation data. This includes published validated methods of analysis as well as compendial analytical methods, together with partial validation data, which only demonstrate suitability of in-house equipment and personnel. If a change in procedure is necessary during the stability trial, data should be generated (and processed), which prove that no statistically significant difference exists between the old and new method of analysis.

The stability-indicating methodology should be validated by the applicant and analytical procedures described in sufficient detail to permit independent validation.

Degradation products

Chromatographic or other analytical methods designed to determine the content of degradation products should be submitted with the assay results, even where an assay procedure specific for the API has been used.

Physical properties

In addition to assaying the API and/or suitable markers and degradation products, it is necessary to ensure that the physical properties of the product are unimpaired after storage. Consideration should be given to the stereo-chemical integrity of the product. Additional tests will vary with the formulation and may include the following:

a) *Tablets and lozenges*

Dissolution rate (single point for immediate release, multipoint for modified release), disintegration time (not required if dissolution rate is done), moisture content, appearance, hardness, friability, colour and odour.

Solubility time and appearance of solution for soluble tablets, dispersion time, fineness of dispersion, dissolution rate (unless the API is in solution after dispersion) for dispersible tablets. Intactness of coating in the case of coated tablets, unless justified.

b) Capsules

Moisture content, colour and appearance (capsule shell and contents), brittleness, disintegration time (when dissolution rate is not applicable) and dissolution rate (single point for immediate release, multipoint for modified release).

When conducting stability trials for solid dosage forms and other products with compendia dissolution requirements and which have a history of bioavailability problems, dissolution rates should be determined.

c) Emulsions and suspensions

Appearance (such as colour and phase separation), odour, pH and viscosity, resuspendability, particle size, sterility for ophthalmic preparations, preserving ability and preservative content.

Test methods to determine particle size should not employ extensive dilution of particles or any other manipulation, which could affect the real particle size existing in the dosage form. The applicability of the particle size dependent variable, such as sedimentation, should also be considered.

After storage, samples of suspensions should be prepared for assay in accordance with the recommended labelling under "Directions for use".

d) *Solutions*

Appearance, pH, viscosity and density, (where relevant), solubility time (reconstitution and appearance thereof) sterility, preserving ability and preservative content (where relevant).
Tests should be performed to ensure compatibility between the container-closure system and the product and the results should be included in the submission.

e) *Powders and granules (including those for reconstitution)*

Moisture content, resuspendability/reconstitution time and appearance of reconstituted product, and microbial limits. The reconstituted product should be tested in accordance with requirements for a solution or suspension.

f) *Metered Dose Inhalation aerosols*

Uniformity of delivered dose, number of metered doses, particle size (suspensions), spray pattern, microbial limits and deposition of emitted dose.

Because the container contents are under pressure, filled containers should be checked for loss in mass over the expiration dating period.

For suspensions, aggregate (or solvate) formation may lead to clogged valves, or the delivery of a pharmacologically inactive dose. Corrosion of the metering valve, or deterioration, may adversely affect the delivery of the correct quantity of API.

g) *Ointments and creams*

Homogeneity, pH, rheological properties, particle size and mass loss (plastic containers). Preserving ability if a preservative is present. Preserving ability of all topical preparations containing corticosteroids.

h) Parenterals

Small volume parenterals include an extremely wide range of preparations and container-closure types. Each should be included in the stability study. Evaluation of these products should include at least the following: pH, particulate matter, pyrogens (containers larger than 15 ml) and syringeability of non-aqueous products.

If uniformity of mass and moisture content for a container of freeze dried product that is reconstituted with solvent prior to administration as an injection, are already controlled, a requirement for loss in mass should not be necessary.

If a validated system exists, sterility will generally not be required to be included in the stability programme. Initial sterility should be recorded on stability reports.

Tests should be performed to ensure the compatibility between the container-closure system and the product, and the results submitted. Aspects to be investigated on the closure include possible pigmentation, resealing following multiple penetration, and force for needle to penetrate.

A brief justification should be included stating the reasons for the container size chosen e.g. largest air volume or largest surface contact, etc. Additional tests include globule size (where applicable), volume (plastic containers), moisture permeability (where applicable) and extractables (plastic containers). Tests should be performed to ensure the compatibility between the container-closure system and the product. These data should be submitted.

i) *Suppositories*

Melting range point, breaking strength and disintegration. The effect of ageing may also be observed from hardening of the suppository base; therefore, control and stability testing should include

disintegration time at 37 ºC. Accelerated studies should be conducted at 2 to 3 ºC below the melting point of the suppositories.

j) Admixtures

For any product intended for use as an additive to another product, the possibility of incompatibilities exists. In such cases, the product that is labelled to be administered by addition to another product (e.g. parenterals, aerosols) should be studied for stability and compatibility in admixture.

A suggested protocol should provide for tests to be conducted at zero-, 6-, 8- and/or 24- hour intervals thereafter. These should include:

- Assay of active substance and any other ingredient for which a limit is set in the final product specification;
- pH (especially for unbuffered LVPs), colour and clarity (particulate matter);
- interaction with the container;
- identification of precipitant/sediment (although the presence of any precipitant indicates that the product is already non-conforming)
- bacterial endotoxins and sterility (reconstituted solution for injection).

k) *Transdermal patches*

Release rate, seal integrity, mass variation and adhesive properties.

Content of Antimicrobial Preservatives

Dosage forms containing preservatives to control microbial contamination should have the preservative content monitored initially (zero time) and at reasonable intervals throughout the projected expiration dating period of the product. This may be accomplished by performing microbial challenge tests (e.g. the Antimicrobial Preservative Effectiveness Test of the USP or BP, which is applicable to unopened containers) and by performing chemical assays for the preservative.

When the minimum quantity of preservative to achieve effective microbial control has been determined for solutions, chemical assays for the full period of the shelf-life may be adequate, provided that the results of tests demonstrating the preservative effectiveness are submitted for evaluation. It is particularly important to consider the adequacy of the preservative system under conditions of use for multidose vials.

When less than full-term data are submitted for registration purposes, or for a major change in formulation, preliminary results for preservative effectiveness include a minimum storage period of nine months at real-time storage conditions or 6 months accelerated conditions for those products for which the effect of ageing on preservative effectiveness needs to be demonstrated, e.g. suspensions, creams.

Those products requiring control of microbial quality, and which do not contain preservatives, should be tested initially (at zero time) and at the termination of study or at the end of the projected expiration dating period according to the final product specification (PART 3F / Section 3.2.P.5) for bio burden.

These tests include, e.g. Microbial limit Tests of the USP or BP, which includes a limit for total microbial count and for absence of *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Salmonella* species).

In addition, it is recommended that topical preparations be controlled for the absence of *Pseudomonas cepacia*, *Aspergillus niger* and *Candida albicans*, as well as any other topical pathogens that may be identified as potentially harmful. Simulated use tests on topical preparations packed in jars, and on ophthalmic preparations, are desirable.

Effects of Opening and Closing Containers

Investigation into “in-use” stability may be important for certain sensitive products. Where applicable, the opening and closing of containers may follow a recommended dosage direction included in the MRF1 PART 1C / Module 1 Section 1.3.

Desiccants

Duration of satisfactory performance of desiccants should be related to the shelf-life/expiry date.

13 REFERENCES

in addition SA guidelines listed under Introduction, Quality guideline 7.05

13.1 Guideline on Stability testing: Stability testing of existing active substances and related finished products (CPMP/QWP/122/02 rev 1 corr)

13.2 Guideline on quality of herbal medicinal products/traditional herbal medicinal products (EMA/HPMC/201116/2005 Rev 2 / EMA/CPMP/QWP/2819/00 Rev. 2)

13.3 Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products (EMA/HMPC/162241/2005 Rev. 2 / CPMP/QWP/2820/00 Rev 2).

13.4 Reflection paper on microbiological aspects of herbal medicinal products and traditional herbal medicinal products (EMA/HMPC/95714/2013)

13.5 Note for Guidance on evaluation of stability data. (CPMP/ICH/420/02)

13.6 Note for Guidance on Stability testing: Stability testing of New Drug Substances and Products (CPMP/ICH/2736/99 corr)

13.7 WHO Technical Report Series, No. 953, 2009, Annex 2

13.8 Guideline on Summary of Requirements for Active Substances in the Quality Part of the Dossier (CPMP/QWP/297/97))

13.9 Note for Guidance on Photostability Testing of New Active Substances and Medicinal Products (CPMP/ICH/279/95)

ANNEX B

NAMING AND LABELLING CONVENTIONS FOR ACTIVE INGREDIENTS IN COMPLEMENTARY MEDICINES

PREAMBLE

Complementary medicines use a wide range of potential active ingredients from numerous sources and disciplines, and have varying traditional and common names, uses and preparation methods. As a result, the many potential active ingredients may vary significantly in their nomenclature. This often leads to situations in which the same active ingredients may be labelled / named in different ways. In order for stakeholders to provide sufficient identifying information of specific active ingredients that would provide sufficient insight into its origin and intention, a standardised approach to naming and labelling active ingredients in CMs is necessary. This will provide for standardised reference and evaluation of applications for registration of CMs and will enhance prescriber and patient choice when selecting a CM best suited for their purposes. This guidance takes into account the challenge associated with limited space available on product labels while stipulating the standard requirements for Professional Information (PIs) and Patient Information Leaflets (PILs).

1. INTRODUCTION

1.1 Objectives of the Guideline

The guideline seeks to standardise the presentation of naming of active ingredients used in these medicines. It represents mechanisms for all labelling that would be deemed most appropriate, however, alternative approaches can be used when there are justifiable reasons.

1.2 Scope of the Guideline

This guideline is applicable to all Complementary Medicines (Category D).

The guideline addresses the format of naming information for active ingredients in CMs and pertains to the labelling of products available for sale, those products yet to be made available for sale and for applications submitted to the SAHPRA in consideration of their registration, based on quality, safety and efficacy.

1.3 General Principles

The requirements for approved and common names in the relevant specified guideline should also be considered. The correct intended layout should make use of square and round brackets and italicisation and capitalisation of the Latin binomial, where appropriate. The use of the Accepted Name is required while the use of the Common Name is optional.

Active ingredients should be included in the following order of priority:

- Discipline-specific active ingredients (where relevant) in order of the highest quantity to least quantity grouped by unit of measure; and
- Health supplement active ingredients in order of the highest quantity to least quantity grouped by unit of measure. Units of measure should reflect those referenced in the relevant annexure of Guideline 7.04.

Any active ingredients of the same quantity should be presented in alphabetical order. The accepted name may / may not be in italics which is determined by the origin of the name. Accepted names should be checked, such that they are precisely representative of the ingredient used, with attention to detail of lettering style and spacing in the required areas critical.

Descriptor use is mandatory if not already described by the approved / common names.

In sections 2 and 3 bracketed text indicated by <blue> brackets represents text that would be inserted. Any black text that appears in the tables represents standard text.

1.3 Glossary

Accepted name: with respect to herbal ingredients, refers to Guideline 7.01, Section 1.5.3, the accepted name is the name for the species accepted by approved international collaborative databases.

> *Reference must be made to the internationally accepted name for the plant, fungus or alga by referring to the following databases where appropriate (in order of priority):*
>
> *a) The Plant List (Available at: http://www.theplantlist.org);*
> *b) The Index Fungorum (Available at: http://www.indexfungorum.org);*
> *c) The International Plant Names Index (Available at: http://www.ipni.org); or*
> *d) other recognised major flora*
>
> *Examples of correct herbal names include:*
>
> • *Olea europaea subsp. africana (*Mill*.)* P.S. Green
> • *Crataegus curvisepala* Lindm*.*
> • *Thymus zygis* subsp*. gracilis (*Boiss*.)* R.Morales ct. thymol

Approved name: with respect to minerals refers to Guideline. 7.01, Section 1.5.3 the 'approved name' – INN – for minerals.

Common name: refers to any one of a number of vernacular names used in everyday language, in any language, for a given species - in contrast to its scientific name which is usually a Latinised binomial and which follows certain conventions. e.g. Dandelion, Buchu, Artichoke

Descriptor: may refer to the method of preparation, part used, source or other description that materially represents the specified ingredient as being different.

Pharmacopoeial name: Pharmacopoeial names are the Latinised names of herbal, animal or other ingredients that are given to ingredients that are fully characterised in a monograph of an accepted pharmacopoeia e.g. *Bulbus allii cepae*, *Rhizoma curcumae longae*, *Radix glycyrrhizae*

2. NAMING CONVENTIONS FOR PROFESSIONAL INFORMATION (PI) AND PATIENT INFORMATION LEAFLETS (PIL)

2.1 General Ingredients in Complementary Medicines

<Accepted/Approved Name> (<Common / Pharmacopoeial Name>) …….. <X> <unit>

e.g. Niacinamide (Vitamin B3)……..30 mg

2.2 Labelling of Biological Substances and Animal Substances

<Accepted/Approved Name> (<Common / Pharmacopoeial Name>) …….. <X> <unit>
[<part, preparation and / or biological descriptor>]

e.g. *Taraxacum campylodes* G.E. Haglund (Dandelion) …….. 200 mg
[root powder]

e.g. Chondroitin sulphate…….. 800 mg
[porcine]

e.g. *Perna canalicula* (Green Lipped Mussel) …….. 100 mg

2.3 Labelling of Herbal Extracts

Option 1

Where: X = Dried herb equivalent

<Accepted name> (<Common Name / Pharmacopoeial Name>) …….. <X> <unit>

[<part, preparation and / or biological descriptor> as <ABC> <unit> of a <D:E> extract / standardised to <Herbal Component Name> <FGH> %]

e.g. *Hypericum perforatum* L. (St. John's Wort) …… 300 mg

[flowering tops, as 30 mg of a 10:1 extract standardised to hypericin 0,3 %]

OR:

Option 2

Where: X = Amount included in formulation

<Accepted name> (<Common Name / Pharmacopoeial Name>) …….. <X> <unit>

[<part, preparation and / or biological descriptor>, <D:E> extract / standardised to <Herbal Component Name> <FGH> % providing <ABC> unit of dried herb equivalent>]

e.g. *Hypericum perforatum* L. (St. John's Wort) …… 30 mg

[flowering tops, 10:1 extract standardised to hypericin 0,3 % providing 300 mg of dried herb equivalent]

2.4 Labelling of Herbal Ingredients with mixed sources

Option 1

<*Genus*> species (<Shared Common / Pharmacopoeial name>) …….. <X> <unit>

[<parts, preparation or biological descriptor>]

from: <Accepted name(s)>

e.g. *Euphrasia* species (Eyebright) …… 1 ml

[aerial portions, 1:10]

from: *Euphrasia officinalis* L., *Euphrasia rostkoviana* Hayne, *Euphrasia stricta* D. Wolff

OR:

Option 2

<Preparation description> of <*Genus*> species (<Shared Common / Pharmacopoeial name>) from:

<Accepted name>

[<parts, preparation or descriptor>]

<Accepted name>

[<parts, preparation or descriptor>]

…

e.g. Tincture of *Crataegus* species (Hawthorn) from:

Crataegus monogyna Jacq.

Crataegus rhipidophylla Gand. (*Crataegus oxyacantha* L.)

[fruits]

2.5 Labelling of Health Supplements

Option 1

<Accepted/Approved Name> (<Common/ Pharmacopoeial Name>) …….. <X> <unit>

providing <descriptor> …….. <X> <unit>

e.g. Chromium polynicotinate…….. 200 mg

providing Chromium (elemental)...……... 20 mg

OR:

Option 2

<Accepted/Approved Name> (<Common/ Pharmacopoeial Name>) …….. <X> <unit>

e.g. L-Ascorbic acid (Vitamin C) …… 100 mg

3. NAMING CONVENTIONS FOR CONTAINER OR PACKAGING LABELS

The same principles may apply in the application of the conventions described in sections 2 and 3. However, due to restrictions and space on the label, it shall be sufficient to use a simple Latin binomial or pharmacopoeial name of herbal ingredients that are fully characterised in a monograph of an accepted pharmacopoeia, provided it is clear to the consumer exactly which herb (or part thereof) or other substance is being used. The common name may also be stipulated and the summarised information regarding the part, preparation and / or biological descriptor must be supplied.

Option 1

<Accepted/Approved Name> (<Common / Pharmacopoeial Name>) …….. <X> <unit>

[<brief description of part, preparation and / or biological descriptor, extract / standardisation>]

OR:

Option 2

Where space limitation on the label may prevent listing of the name as per option 1.

<Accepted/Approved Name> (<Common/Pharmacopoeial Name>, <brief description of part/preparation/source>) …….. <X> <unit>

[<extract / standardisation>]

OR:

<Common/Pharmacopoeial Name>, <brief description of part/preparation/source>…….. <X> <unit>

[<extract / standardisation>]

OR:

<Common/Pharmacopoeial Name>, <brief description of part/preparation/source>…….. <X> <unit>

providing:

<specified substance>..... <X> <unit>

<specified substance>..... <X> <unit>

OR:

<Preparation description> mix of:

<Common/Pharmacopoeial Name, part> …….. <X> <unit>

<Common/Pharmacopoeial Name, part> …….. <X> <unit>

<Common/Pharmacopoeial Name, part> …….. <X> <unit>

OR:

<Elemental name/Salt> (<Source>)..... <X> <unit>

4. ADDITIONAL EXAMPLES

The examples below are not intended to be examples of real formulas but are intended to guide the principles of naming active ingredients only.

4.1 Aromatherapy

PI and PIL:

Volatile oil mix of:

Lavandula angustifolia Mill. (Lavender) …….. 3 ml
[flowers and leaves]

Melaleuca alternifolia (Maiden & Betche) Cheel (Tea Tree) …….. 2 ml

Rosmarinus officinalis L. (Rosemary) …….. 1 ml

Container Label:

Same as for PI and PIL unless space is restricted:

Volatile oil mix of:

Lavender, flowers and leaves …….. 3 ml

Tea tree …….. 2 ml

Rosemary …….. 1 ml

4.2 Ayurveda

Example 1:

PI and PIL:

Withania somnifera (L.) Dunal (Asvagandha) …… 500 mg
[root powder]

Container Label:

Same as for PI and PIL unless space is restricted:

Withania somnifera (L.) Dunal …… 500 mg
[root powder]

OR:

Asvagandha, root powder …… 500 mg

Example 2:

PI and PIL:

Withania somnifera (L.) Dunal (Asvagandha) ……. 1 000 mg
[root, as 0,5 ml of a 2:1 ethanolic extract standardised to withanolides 5 %]

Container Label:

Same as for PI and PIL unless space is restricted:

Withania somnifera (L.) Dunal ……. 1 000 mg
[root, as 0,5 ml of a 2:1 ethanolic extract standardised to withanolides 5 %]

OR:

Asvagandha, root ……. 1 000 mg (DHE)*
* Dried Herb Equivalent

4.3 Homeopathy

Example 1:

PI and PIL:

Sepia officinalis (Common cuttlefish)	4 cH	……..	0,3 ml
Astacus astacus (*Astacus fluviatilis*)	6 cH	……..	0,3 ml
Lycopodium clavatum L.(*Lycopodium clavatum*)	6 cH	……..	0,3 ml
Strychnos nux-vomica L. (*Nux vomica*)	12 cH	……..	0,3 ml
Citrullus colocynthis (L.) Schrad. (*Colocynthis*)	30 cH	……..	0,3 ml
Potassium carbonate (*Kalium carbonicum*)	30 cH	……..	0,3 ml

Container Label:

Same as for PI and PIL unless space is restricted:

Sepia officinalis	4 cH	……..	0,3 ml
Astacus fluviatilis	6 cH	……..	0,3 ml
Lycopodium clavatum	6 cH	……..	0,3 ml
Nux vomica	12 cH	……..	0,3 ml
Colocynthis	30 cH	……..	0,3 ml
Kalium carbonicum	30 cH	……..	0,3 ml

Example 2:

PI and PIL:

Sepia officinalis (Common cuttlefish) D4 …….. 0,3 ml

Astacus astacus (*Astacus fluviatilis*) D6 …….. 0,3 ml

Container Label:

Same as for PI and PIL unless space is restricted:

Sepia officinalis D4 …….. 30 mg

Astacus fluviatilis D6 …….. 30 mg

Example 3:

PI and PIL:

Calendula officinalis L. (*Calendula officinalis*) Mother Tincture …….. 30 ml

[HAB 3A: 60 % alcohol]

Container Label:

Same as for PI and PIL unless space is restricted:

Calendula officinalis MT…….. 30 ml

[HAB 3A: 60 % alcohol]

4.4 Traditional Chinese Medicine

Example 1:

PI and PIL:

Poria cocos (Schwein.) F. A. Wolf (Fú líng) …… 500 mg
[sclerotium powder]

Container Label:

Same as for PI and PIL unless space is restricted:

Fú líng …… 500 mg
[sclerotium powder]

Example 2:

PI and PIL:

Reynoutria multiflora (Thunb.) Moldenke (*Polygoni multiflori radix preparata*) ……. 1 000 mg
[root, as 50 mg of a 20:1 extract]

OR:

Reynoutria multiflora (Thunb.) Moldenke (zhì hé shǒu wū) ……. 1 000 mg
[root, as 50 mg of a 20:1 extract]

Container Label:

Same as for PI and PIL unless space is restricted:

Polygoni multiflori radix preparata ……. 1 000 mg
[root, as 50 mg of a 20:1 extract]

OR:

zhì hé shǒu wū ……. 1 000 mg
[root, as 50 mg of a 20:1 extract]

4.5 Unani

PI and PIL:

Nardostachys jatamansi (D.Don) DC. (Sumbul-ut-teeb) …… 300 mg
[rhizome powder]

Container Label:

Same as for PI and PIL unless space is restricted:

Sumbul-ut-teeb …… 300 mg
[rhizome powder]

4.6 Western Herbal Medicine

Example 1:

PI and PIL:

Inula helenium L. (Elecampane) …… 250 mg
[root powder]

Container Label:

Same as for PI and PIL unless space is restricted:

Inula helenium L. …… 250 mg
[root powder]

OR:

Elecampane …… 250 mg
[root powder]

Example 2:

PI and PIL:

Ginkgo biloba L. (Ginkgo) …….. 120 mg

[leaf, 50:1 extract standardised to ginkgo flavone glycosides 24 % and terpenoids 6 % providing 6 000 mg of dried herb equivalent]

Container Label:

Same as for PI and PIL unless space is restricted:

Ginkgo biloba L. (Ginkgo, leaf) …….. 6 000 mg (DHE)*

* Dried Herb Equivalent

4.7 Health Supplements

Example 1:

PI and PIL:

Magnesium ascorbate……		200 mg
providing	Vitamin C…….	164 mg
	Magnesium……..	12 mg

Container Label:

Same as for PI and PIL unless space is restricted:

Vitamin C (as Magnesium ascorbate) ……..	164 mg
Magnesium (as Magnesium ascorbate)…….	12 mg

Example 2:

PI and PIL:

Copper (ii) bisglycinate……	200 mg
providing Copper…….	20 mg

Container Label:

Same as for PI and PIL unless space is restricted:

Copper (as copper (ii) bisglycinate)……...	20 mg

Example 3:

PI and PIL:

Calcium pantothenate……..... 5 mg
providing Pantothenic acid (Vitamin B5)

Container Label:

Same as for PI and PIL unless space is restricted:

Panthothenic acid (Vitamin B5)…… 5 mg

OR:

Vitamin B5 (as calcium pantothenate)..... 5 mg

Example 4:

PI and PIL:

Cyanocobalamin (Vitamin B12) …… 2,4 mg

Container Label:

Same as for PI and PIL unless space is severely restricted:

Vitamin B12 …… 2,4 mg

Example 5:

PI and PIL:

L-Ascorbic acid (Vitamin C)..... 100 mg

Container Label:

Same as for PI and PIL unless space is severely restricted:

Vitamin C..... 100 mg

Example 6:

PI and PIL:

Sardina pilchardus (European Pilchard) oil..... 500 mg
providing:
Eicosapentaenoic acid (EPA)..... 80 mg
Docosahexaenoic acid (DHA)..... 52 mg
Total Omega 3 fatty acids..... 150 mg

Container Label:

Same as for PI and PIL unless space is restricted:

European Pilchard oil.....……. 500 mg
providing:
EPA..... 80 mg
DHA..... 52 mg
Total Omega 3..... 150 mg

Example 7:

PI and PIL:

Oenothera biennis L. (Evening Primrose) oil....…… 500 mg
providing:
Linoleic Acid (LA)..... 80 mg
Gamma-Linolenic Acid (GLA)..... 52 mg

Container Label:

Same as for PI and PIL unless space is restricted:

Evening Primrose oil....……...…….. 500 mg
providing:
LA..... 80 mg
GLA..... 52 mg