agriculture,
forestry & fisheries

Department:
Agriculture, Forestry and Fisheries
REPUBLIC OF SOUTH AFRICA

DIRECTORATE: AGRICULTURAL INPUTS CONTROL

PHARMACEUTICAL AND ANALYTICAL GUIDELINES STOCK REMEDIES

This guideline is intended to provide recommendations to applicants wishing to submit applications for the registration of Stock Remedies. It represents the DAFF's current thinking on the quality, safety and efficacy of Stock Remedies. It is not intended as an exclusive approach. DAFF reserves the right to request any additional information to establish the safety, quality and efficacy of a stock remedy in keeping with the knowledge current at the time of evaluation. Alternative approaches may be used but these should be scientifically and technically justified. DAFF is committed to ensure that all registered stock remedies will be of the required quality, safety and efficacy. It is important that applicants adhere to the administrative requirements to avoid delays in the processing and evaluation of applications. Guidelines and application forms are available from the office of the Registrar and DAFF website. This guideline is based on the VICH and MCC guidelines, with only minor modifications.

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1. INTRODUCTION

The requirements for pharmaceutical and analytical information are in part B of the dossier and relevant information from Part B must be FULLY AND ACCURATELY completed in each application form, as indicated.

Please note: Dossiers may be submitted in the format required in the country of origin, if it is the format required by an internationally recognised regulatory body.

However, all sections relevant to the pharmaceutical and analytical data requirements must be submitted to the Registrar: Act 36 of 1947.

Exemption must be requested and scientific justification provided for any deviations from the format as required by the Registrar: Act 36 of 1947.

The sections of Part A are as follows:

PART A1 GENERAL INFORMATION

Please refer to the Guidelines for Stock Remedy Data Requirements.

The sections of part B are as follows:

PART B1 Active Pharmaceutical Ingredient (API)

PART B2 Formulation

PART B3 Raw material specifications and control procedures

PART B4 Containers and packaging materials

PART B5 Manufacturing procedure
PART B6 Finished product
PART B7 Stability data
PART B8 Analysis
PART B9 Pharmaceutical development

NOTE: DATA MUST BE COMPILED IN THIS ORDER

The above Parts should be read together with the following relevant guidelines:

Stability: refer to Stability Guidelines for Stock Remedies.

Bioequivalency studies and/or clinical studies: refer to VICH and/or other relevant guidelines.

Vaccines: refer to Veterinary Biologicals Guidelines for Stock Remedies.

(The applicant may also refer to other internationally acceptable guidelines such as VICH, EMA, WHO/FAO, OIE, USDA/FDA, APVMA, SAHPRA guidelines).

2. SUMMARY OF DOSSIER

The Quality Overall Summary (QOS) or Pharmaceutical Expert Report (PER) should include sufficient information to provide the reviewer with an overview of PART B. The QOS should also emphasise critical key parameters of the product, for instance, justification in cases where guidelines were not followed.

3. PART B SECTIONS 1 - 9 PHARMACEUTICAL AND ANALYTICAL REQUIREMENTS

Ensure that the administrative details i.e. applicant, proprietary name of the medicine, dosage form, manufacture and manufacturer details and composition correspond with the details submitted in the application form. All application forms must be **fully** completed, initialled and signed.

PART B1 ACTIVE PHARMACEUTICAL INGREDIENT (API)

B.1.1 The approved name, or International Non-proprietary Name (INN), or chemical description of the API(s), should be stated, including the structural formula (indicating stereochemistry where appropriate), systematic name, the empirical formula and the relative molecular mass.

The approved name should be the same as the name reflected on PI, label and application form.

B.1.2 The solubility of each API should be stated in terms of a unit part of the substance per number of parts of the solvent, or in unit mass of substance in a given volume of solvent, at a specific temperature. The solvents should include water and the solvent(s) relevant to the product formulation.

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

B.1.3 The storage requirements for the API as specified by the manufacturer of the API and/or prescribed in the pharmacopoeia or acceptable standard reference should be stated and a description of the API container closure system must be included. If a specific storage temperature is not specified in any

acceptable reference, an instruction to protect from excessive heat, freezing and moisture and light should be included unless justified.

B.1.4 The name, business and physical address of each manufacturer of the API being applied for (including any intermediate manufacturer) should be stated. No API from any manufacturer, other than the approved manufacturer(s), may be used.

B.1.5 The Active Pharmaceutical Ingredient File (APIF), or the open part of the DMF, should be submitted in the dossier and should include the following information:

a) The name and physical address of the manufacturer (including any intermediate manufacturer).

b) The approved/INN name of the relevant API.

c) The chemical name and chemical structure of the API.

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

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

Critical Steps: Tests and acceptance criteria (with justification including experimental data) to ensure that the process is controlled should be provided.

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

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

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

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

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

e) Structure (including stereochemistry) elucidation for new chemical entities (NCEs). Proof of correctness of structure for a well-known API, e.g. IR spectrometric comparison against an official standard may be acceptable. In the case of enantiomers an additional test is required to confirm its identity (pharmacopoeial). If the API is not described in a monograph of any of the official pharmacopoeias, no official standard is available in which case sufficient evidence (NMR, IR, MS, elemental analysis, etc., with interpretation) should be provided in support of the structure and stereochemistry.

f) A description of impurities, indicating the possible source of impurities and a clear distinction between actual and possible impurities.

g) A description of possible degradation products.

h) The physical and chemical properties of the API, including e.g. solubility, particle size hygroscopicity.

i) The specification in tabulated format, not narrative, with detailed methods used for quality testing (identification, assay, determination of related substances, residual solvents etc., including chromatograms for the API Manufacturer and FPP Manufacturer (if different). When pharmacopoeial methods are used these should be current.

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

If this information is the same as that which is included in PART B.3 Raw material specifications cross-referral to PART B.1 may be included in PART B.3.

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

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

k) Reference standards:

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

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

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

Secondary standards should always be established against the pharmacopoeial/primary standard.

l) A description of the container-closure system.

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

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

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

m) Results of stability studies performed on the API obtained by the above route of synthesis when stored in the proposed container closure system. The conditions under which degradation products are formed (stress testing). A validated stability-indicating assay method, described in full, should be used in these studies, unless the method for related substances is specific and

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

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

o) The proposed retest period.

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

B.1.6 A valid EU certificate of suitability (CEP) may be submitted if available.

The CEP certifies the suitability of the relevant Ph. Eur. monograph to control the quality of the API produced by the manufacturer specified in the CEP. The Ph. Eur. must be used for API specifications and procedures if a CEP is submitted.

Please ensure that the CEP is accompanied by any annexes mentioned in the CEP. Any additional requirements indicated in the CEP and the methods described in the annexes are officially part of the API specification. Also ensure that the declaration of access is completed.

If a CEP is submitted, detailed descriptions of the methods of synthesis and analysis of the API are not required.

Impurities and residual solvents listed in the CEP should be included in the API specifications (PART B3).

It is the responsibility of the applicant to be aware of changes in the status of CEPs that are used for their products and to notify Council accordingly. It is also the responsibility of the applicant to ensure that the revised CEP is obtained from the CEP holder when applicable and to submit such updated CEP.

If the CEP is withdrawn or suspended for whatever reason a DMF or APIF should be submitted within six months, together with the reason for withdrawal/suspension of CEP

The validity of the CEP can be verified under “Certification” at:

http://www.edqm.eu/site/Databases-10.html

In addition:

a) Any information required for the APIF but not addressed in the CEP must be submitted, e.g. physico-chemical properties.

b) If the retest period is not reflected in the CEP, stability data generated according to the Stability guideline and/or supporting literature to demonstrate the API stability should be submitted.

c) Certificates of Analysis (CoAs) from the API manufacturer relating to at least two batches should be included (dated, signed on letterhead).

B.1.7 If more than one manufacturer of the API is being applied for (irrespective of the apparent similarity of the routes utilised by the different manufacturers), or when different routes of synthesis are used in the manufacture of the API, the following should be submitted:

a) An APIF or DMF or CEP as above, for each API manufacturer.

b) 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.

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

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

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

A report, signed and dated, is required addressing the above information.

d) Confirmation of compliance with the Stability guideline and identification of the relevant data in the dossier.

B.1.8 If an identical route of synthesis, or manufacturing process of the PPL (in case of Biological Medicines), including the purification step is used by each site of **the same parent company,** a statement to this effect will suffice with regard to the route.

In this case include valid CoAs from the API manufacturer or manufacturer of the primary production lot (in case of Biological Medicines) for two batches issued by each site.

B.1.9 Starting materials for *in situ* API preparation are treated as APIs.

B.1.10 For a mixture of API(s) or API(s) with IPIs, the blending of the ingredients is considered as the first step in the manufacture of the final product, and therefore does not fall under the definition of an API even though it may take place in a different facility. The resultant mixture, or partially completed final product e.g. coated or uncoated granules, is regarded as an FPP intermediate.

The only exceptions can be made where the API cannot exist on its own, e.g. due to insufficient stability without a stabilising agent.

The Ph.Eur., USP, BP include these (e.g. moxidectin) and other APIs contained in veterinary remedies. Veterinary Pesticides can be researched in the Pesticide Manual, FAO guidelines and Agricultural Remedy guidelines which may be more applicable (with the exception of those for oral use).

The mixing of the API with an IPI or another API thus forms part of the manufacturing procedure of the final product which is addressed in PART B5, whilst the API(s) used in such mixtures should be included in PART B1, according to the requirements of 3.1.5 or 3.1.6. The formulation, API and IPI specifications and control procedures, packaging materials, stability and pharmaceutical development of the FPP intermediate are addressed in PARTs B5, B1, B3, B4, B7 and B9 respectively in accordance with the requirements of the relevant PARTs.

PART B2 FORMULATION

The use of IPIs that are not described in official pharmacopoeiae is strongly discouraged and should be justified. For flavourants, fragrances, colourants and inks refer to **The Foodstuffs, Cosmetics and Disinfectants Act, Act 54 of 1972**

B2.1 The formulation should show the INN or approved names, and/or chemical names of all APIs, and polymorph (if relevant) and approved names of inactive pharmaceutical ingredients (IPIs), including those that do not remain in the final product after manufacturing e.g. granulating agents and gases used for flushing. IPIs not present in the final product should be indicated.

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

B2.2 The name and the quantity of the API and the name and quantity stated under "Composition" in the package insert, label and application form should correspond. The name and quantity of the API per dosage unit should also correspond to the final product specifications.

Justification should be provided for deviations.

The theoretical quantity of the base of the API should be stated if a compound, e.g. hydrate, solvate, salt is used. If the moisture content or other characteristic of an API is relevant to the quantity of the IPIs used in the formulation, this should be mentioned in a footnote.

B2.3 A product may contain more than one API provided that:

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

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

c) the product provides rational concurrent therapy for a significant proportion of the target population, e.g. combinations of dips, pour-ons and anthelmintics.

B2.4 Each pharmaceutical ingredient should be listed with its quantity per dosage unit. This would include the vehicle(s), solvent(s) or base(s) (excluding quantities of coating solvents). In the absence of an approved name (INN) or chemical name, a chemical description or characterisation of the substance,should be given. If so required and relevant, the proprietary name of the IPI may be included in addition to the approved name.

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

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

The grade of IPIs, also when a pharmacopoeial monograph covers more than one grade, and the type of water, where relevant, should be indicated.

B2.5 The purpose of each IPI should be stated briefly. If the IPI is used for multiple purposes in the formulation, each purpose should be mentioned.

The name of each API and IPI should correspond and the quantities correlate with those reflected in the batch formulation submitted in PART B5 and the batch manufacturing record submitted or made available for inspection.

B2.6 Some IPIs are single chemical entities while others are combinations. Some are chemically transformed, e.g. modified starch. For excipients that are mixtures of chemically related or unrelated components, e.g. polyol esters (mixture of mono, di and triesters), direct compression excipients, solutions or film coating formulations, or excipients that are chemically modified, the nature and quantity of each such excipient should be specified.

The qualitative composition of inks should be specified.

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

B2.7 Any overages for the API should be stated separately. The label claim quantity should be stated and the excess quantity indicated as the actual quantity or as a percentage. For example, 500 mg + 5 mg (= 1 %) overage* **Percentage overage may not exceed 5%.**

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

The reason for the overage should be stated / justified, e.g. with reference to batch results, in PART B9.

B2.8 If a potency adjustment for the API has to be made, a statement to the effect that the actual quantity of the active will depend on the potency and the IPI(s) that will be used to adjust the bulk quantity should be made. The manner in which the adjustment will be made should also be specified.

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

B2.9 Permitted flavouring and colouring agents (that comply with The Foodstuffs, Cosmetics and Disinfectants Act, Act 54 of 1972 or with directives of the EU or the register of the FDA), because of their complexity in many instances, may be described in terms of their main constituents only, provided that conclusive identification is given in the relevant section. The Colour Index Numbers (Foodstuffs, cosmetics and disinfectants Act, 1972 Regulation Food Colourants) or the colourant reference number in accordance with the EU directive of colourants should be included in the formulation. The use of dyes, printing ink, coating materials, flavourants and organic solvents is subject to the same safety and quality requirements that apply to medicinal substances.

B2.10 If a vehicle is added up to the required volume or mass of the product, the actual or estimated quantity of that vehicle may be stated. Expressions such as “add up to” and “q.s.” are however acceptable. Solutions added to adjust the pH should be described in terms of composition and strength (e.g. normality, molarity), but it is not necessary to state the actual quantity added as none or only minute quantities may be required.

B2.11 In the case of capsules, the fill mass as well as the capsule size, composition and mass should be indicated.

B2.12 The theoretical mass must be indicated for uncoated tablets. In the case of coated dosage forms, the theoretical mass of the core, coating material, as well as the total mass of the dosage form/unit should be indicated and the IPIs used for each should be grouped separately.

B2.13 For biological medicines, the details of any solution supplied by the manufacturer for the reconstitution before use of a dried biological medicine that is offered for sale in a dried form, should be supplied.

B2.14 Toxicity levels per dosage unit should be indicated for all solvents and for other ingredients when required by The Registrar: Act 36 of 1947. Levels should be indicated as per the most recent edition of the Martindale The Complete Drug Reference.

PART B3 SPECIFICATIONS AND CONTROL PROCEDURES FOR PHARMACEUTICAL INGREDIENTS/RAW MATERIALS

B3.1 Specifications (titles and the limits) of all the active and 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 Registrar: Act 36 of 1947. In the latter case, copies of the relevant monographs should be included.

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

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

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

B3.2 Functionality specifications which confirm the IPI characteristics should be indicated.

B3.3 Additional specifications e.g. isomers, chirality, polymorphs, as well as impurities, particle size distribution, residual solvents, where relevant, should be submitted for all APIs.

B3.4 Control procedures for all active and 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.

B3.5 Specifications and the control procedures for the particle size of APIs which have a low solubility in water should be submitted and the solubility quantified unless justified. Particle size should be stated in SI units (μm). Exemption from this requirement may be granted if the API is administered as a clear solution.

B3.6 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.

B3.7 The following minimum requirement should be confirmed and the name and physical address of the laboratory (ies) performing the tests stated:

a) Identification and assay of the API will be performed irrespective of the possession of a CoA from the manufacturer.

b) Identification of the IPI will be performed irrespective of the possession of a CoA from the supplier.

c) Any tests included in the specifications and not included in a valid CoA will be performed.

B3.8 For IPIs for which a conclusive identification test is not described, all parameters that are specific to the identification of such ingredients should be listed and the tests performed irrespective of the possession of a CoA from the supplier.

B3.9 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)].*

B3.10 Empty capsule specifications should include the description, moisture content, disintegration time and microbial limits.

B3.11 The absence of diethylene glycol should be specified for propylene glycol and glycerine if the dosage form is for oral or parenteral administration.

B3.12 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.

B3.13 The approved name of each ingredient should concur with that reflected in the formulation in PART B2.

B3.14 Novel excipients - 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.

B3.15 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.

PART B4 CONTAINERS AND PACKAGING MATERIALS

B4.1 The immediate container specifications (titles and limits), including the nature of the material, dimensions and sketches where applicable, as well as those of patient ready packs, the closure system, wadding and any other component in direct contact with the product, where applicable, and a description of the control procedures, should be supplied.

These should include the

- moisture and gas permeability of PVC, if not already supported by real time stability data of the product (not relevant for PVC forming a base layer of aluminium blisters) and
- heat seal bond strength / intactness of the blister (integrity of the seal) - PART 3E may be referred to.

B4.2 A description of the control procedures performed by the manufacturer of the final product should be given.

B4.3 A brief description of the outer container, if any, should also be given. At least the nature of the material should be mentioned, e.g. outer cardboard carton.

B4.4 The description of the container and that reflected in the application form and in the stability studies should correspond.

B4.5 If the product is packed in bulk containers, the type of material of the container should be stated.
The maximum period that the product may be stored (bulk) before final packaging should be given in PART B5 the nature of the container should be given in PART B4 and supporting data provided in PART B7.

B4.6 The type of material and the dimensions, including sketches of ampoules, vials, aerosols, applicators and administration sets should be given. Sketches of containers for oral dosage forms and blister packs are not required.

B4.7 All pack sizes should be described in the submission.

B4.8 If equivalent or more protective **immediate container packaging material** than used in stability testing or approved, is applied for, data to substantiate the claim should be submitted, e.g. USP permeation test.

PART B5 MANUFACTURING PROCEDURE

B5.1 An inspection flow diagram, also for FPP intermediates, clearly indicating the sites and processes, including clear distinction between primary and secondary packers, should be included.

B5.2 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.

B5.3 The following should be submitted:

- A comprehensive flow diagram, detailing the various stages of manufacturing -
- A comprehensive description of the manufacturing procedures detailing the various stages of manufacturing - derived from the master manufacturing documents.
  The type and size of manufacturing equipment (including sieve sizes in metric units), duration of treatment, temperature, light and humidity conditions, machine settings (e.g. rotation speed or rpm) and other relevant detail should be indicated.
- A brief description of the packaging procedure.
- A brief description of the packaging procedure reflecting the stages, temperature, humidity and other conditions applicable for the packaging of specific dosage forms e.g. granules should be included.
- For sterile manufacturing the grades of clean areas should also be indicated.

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

In addition:

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

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. If all the stages of manufacturing and packaging are performed at one site, a statement confirming this will suffice.

B5.4 A process validation protocol (VP) or report (VR) should be submitted.

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, grading 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.

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. The VP as well as the VR should then be submitted.

PART B6 FINAL PRODUCT SPECIFICATIONS AND CONTROL

Specifications

B6.1 Specifications (titles and limits) should be listed for in-process controls, FPP intermediate controls, final product controls (batch release), stability controls and the reconstituted or diluted final product (if applicable). [If the in-process controls are submitted in PART B5 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.

B6.2 The limits and acceptance criteria for each parameter (physical, chemical and if applicable microbial) should be fully described, to state "complies" for acceptance criteria is not acceptable.

Assay / content

B6.3 The limits of acceptance for the content of each active ingredient should be expressed as a percentage of the label claim. Limits greater than 5,0 % of the label claim should be justified if not vitamins.

B6.4 Uniformity of dosage units should be in accordance with the general requirements of the current editions of the official pharmacopoeiae. Note that the uniformity has been harmonized in the VICH region (see VICH guidelines). Also refer to European or USA guidelines.

FPP intermediates, including parenterals, should also be evaluated for homogeneity.

Preservative efficacy

B6.5 The preservative efficacy of relevant dosage forms and/or presentations, e.g. multi-dose vials, eye drops, should be specified in PART B6 and presented in PART B7. However, once established for the lowest limit of preservative content specification, it is not a routine batch test requirement.

Control procedures

B6.6 All control procedures, other than those from a recognised pharmacopoeia, should be described in full and calculations included where relevant. If an analysis is not technologically possible, e.g. complex extracts, a motivation and alternative quality criteria should be submitted and discussed.

Certificate of Analysis

B6.7 Complete batch analysis data for at least two batches (pilot or production) of the final product should be submitted with the application.

PART B7 STABILITY DATA

(To be read in conjunction with Stability Guidelines for Stock Remedies)

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.

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

PART B8 ANALYSIS

Validation

B8.1 The full validation data of the assay method of the API related to batch release should be submitted. Chromatograms confirming the separation of the API from the degradation products, if relevant, should be included.

- 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 (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, for the validation should be submitted.

B8.2 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.

Endotoxins

B8.3 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.

B8.4 If the endotoxin levels are not determined according to the method in a recognised pharmacopoeia, the validation data should be submitted for evaluation.

Imported products

B8.5 For imported products at least the identification and assay of the API content should be performed by an approved laboratory (FPRC) after importation. This is to verify that the product has not been affected adversely during transportation. Exemption from this requirement may be applied for if scientific proof and motivation can be provided.

Final release criteria

B8.6 The final non-analytical release criteria should include the verification of the appearance of the dosage form, the container, the package insert, the label, the batch number, the expiry date of the product, the certificate of analysis (including re-analysis for imported products) and the batch release documents (batch manufacturing record compliance) (Final Product Release Responsibility or FPRR functions).

PART B9 PHARMACEUTICAL DEVELOPMENT

B9.1 Any differences in the formulation during the development must be clearly indicated.
A table with a comparison of the batches used in stability and efficacy testing (e.g. clinical / biostudies) and validation, indicating batch types and sizes, manufacturing date(s), batch numbers, and source of API, and confirmation that these batches were prepared according to the final formulation as presented in PART 3B, must be submitted. If this information is not included in the development report, it must be included separately.

B9.2 A description or separate Pharmaceutical Development Report (generally of not more than 25 A4 pages) should be submitted where relevant e.g. NCEs

4. LIST OF ACRONYMS

AMRP	Abbreviated Medicines Registration		
API	Active Pharmaceutical Ingredient	GRN	Goods Received Notice
APIF	Active Pharmaceutical Ingredient File	ICH	International Conference on Harmonisation
BP	British Pharmacopoeia		
BSE	Bovine Spongiform Encephalitis	IPI	Inactive Pharmaceutical Ingredient
CEP	European Certificate of Suitability	MCC	Medicines Control Council
	(Certificate Europeans Propriate)	NCE	New Chemical Entity
CoA	Certificate of Analysis	NTI	Narrow Therapeutic Index
cGMP	Current Good Manufacturing Practices	Ph Eur	European Pharmacopoeia
CV	Curriculum Vitae	SBRA	Summary basis for registration application
DMF	Drug Master File	SOP	Standard Operating Procedure
EU	European Union	TSE	Transmissible Spongiform Encephalopathy
EMEA	European Medicines Agency	USP	United States Pharmacopoeia
FDA	Food and Drug Administration (USA)	USP DI	United States Pharmacopoeia Drug Index
FPRC	Final Product Release Control	VP	Validation Protocol
FPRR	Finished Product Release Responsibility	VR	Validation Report

FPP	Finished Pharmaceutical Product	VICH	Veterinary International Conference on Harmonisation

5. TERMINOLOGY

Active Pharmaceutical Ingredient

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

Final product

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

Finished pharmaceutical product (FPP)

A product that has undergone all stages of production, including packaging in its final container and labelling.

Inactive pharmaceutical ingredient (IPI)

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

Manufacture (manufacturing)

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

Medicinal product

See pharmaceutical product.

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.

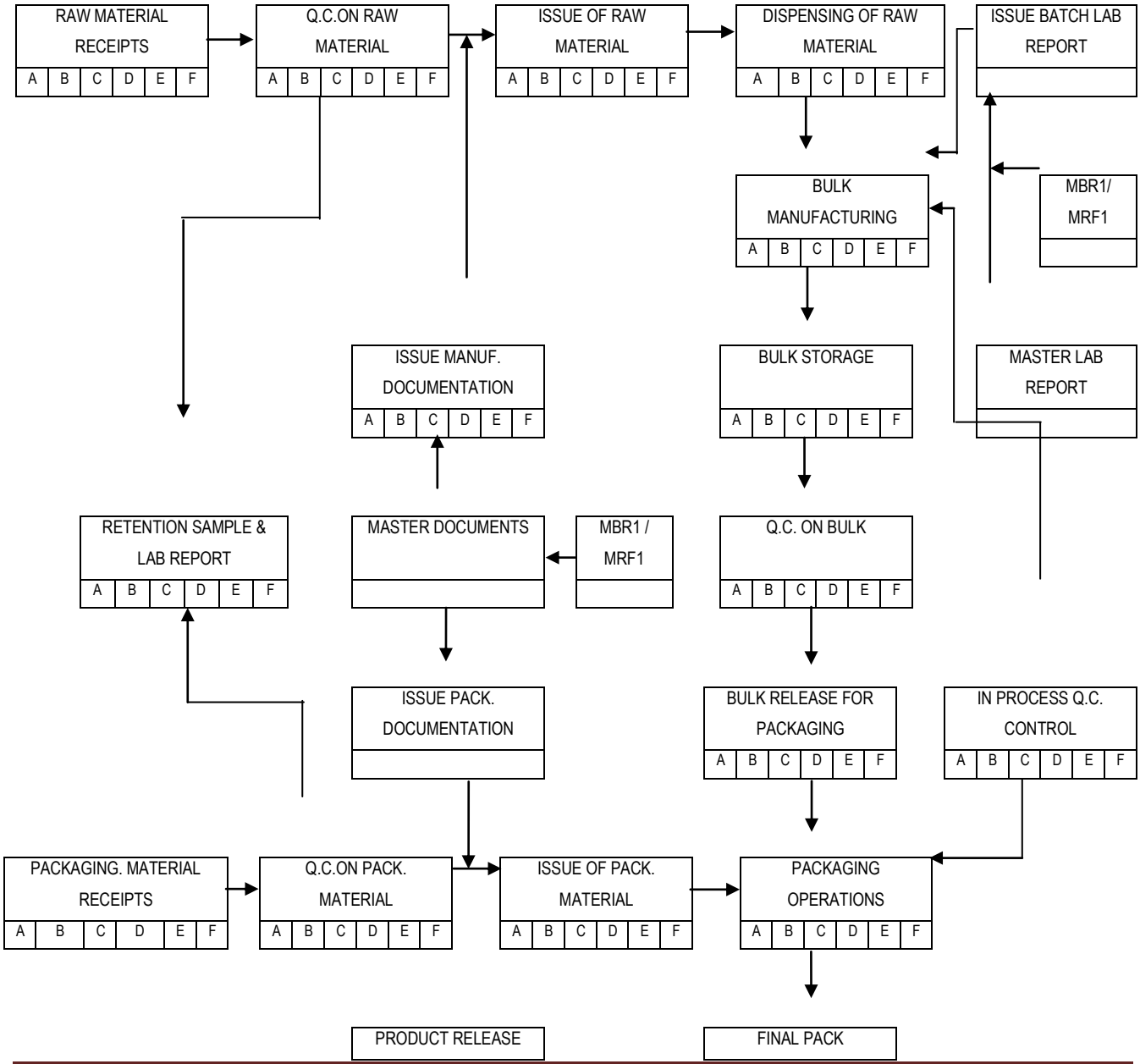
INSPECTION FLOW DIAGRAM OF MANUFACTURED PRODUCTS

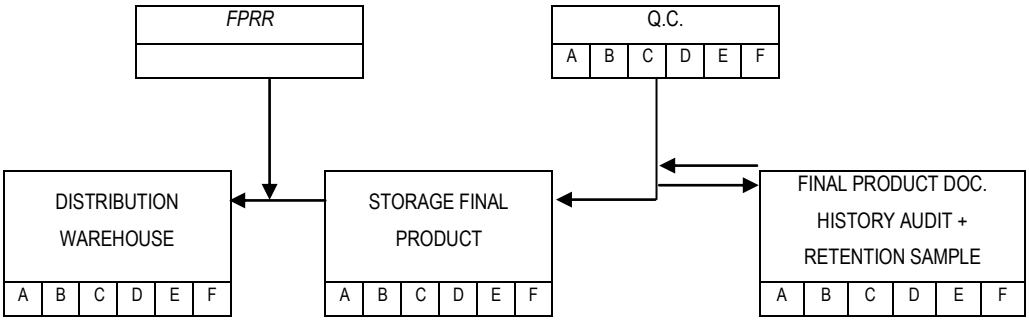
PRODUCT DETAILS

Product Name :
Reg. no. :
PHCR/Applicant :
Dosage form :
Strength(s) :
Pack sizes(s) :

LOCATION

A :
B :
C :
D :
E :
F :





REFERENCES

All the information and guidelines listed below may be referred to in data dossiers. Such information may be valuable to both the applicant and evaluator.

The applicant may also refer to guidelines not referred to hereunder, but which are internationally accepted.

The use of the VICH guidelines is encouraged in terms of international harmonisation.

Guidelines from other countries with which South Africa aligns itself with such as USA (USDA/FDA), EMEA, VICH, FAO/WHO, EDQM, OIE, Australia, Japan, Canada, New Zealand, etc. may be used.

1 The Fertilizers, Farm Feeds, Agricultural Remedies and Stock Remedies Act, 1947. Act No. 36 of 1947)

2 The Fertilizers, Farm Feeds, Agricultural Remedies and Stock Remedies Act, 1947. (Act No. 36 of 1947) Stock Remedy Regulations, Government Gazette No. 29241 (No. R956), Department of Agriculture, 29 September 2006

3 SAHPRA/MCC Pharmaceutical and Analytical Guidelines

4 VICH Guidelines

5 WHO Norms, standards and guidance for pharmaceuticals

6 OIE Manuals

7 EMA Guidelines on Veterinary Pharmaceuticals

8 CPMP Note for Guidance on Development of Pharmaceutics (CPMP/QWP/155/96)