agriculture, forestry & fisheries

Department:
Agriculture, Forestry and Fisheries
REPUBLIC OF SOUTH AFRICA

DIRECTORATE: AGRICULTURAL INPUTS CONTROL

GUIDELINES
DATA REQUIREMENTS FOR STOCK REMEDIES

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1. INTRODUCTION AND OBJECTIVE

This guideline is intended to outline procedures and specific data requirements for registration applications of Stock Remedies under the Fertilizers, Farm Feeds, Agricultural Remedies and Stock Remedies Act, (Act No. 36 of 1947), (hereafter referred to as Act 36/1947) for use in animals.

This document has been prepared by the Directorate: Agricultural Production Inputs API: Stock Remedies Technical Advice, Department of Agriculture, Forestry and Fisheries (DAFF). It provides guidance to applicants on the required data that must be submitted to support an application for the registration of a Stock Remedy.

The purpose of registration is to ensure that all stock remedies meet acceptable standards of quality, safety and efficacy before they are manufactured for distribution and sale in South Africa.
Registration of stock remedies involves consideration of requirements as stipulated in the Fertilizers, Farm Feeds, Agricultural Remedies and Stock Remedies Act, 1947 (Act No. 36 of 1947) and its regulations. Applicants must ensure that they are aware of their obligations in terms of this Act and regulations, as well as other Acts which may be relevant to Stock Remedies.

Other related Acts include, but not limited to:

- Animal Diseases Act, 1984 (Act No 35 of 1984).
- Medicines and Related Substances Control Act, 1965 (Act No 101 of 1965, as amended by Act 90 of 1997).
- Foodstuffs, Cosmetics and Disinfectant Act, 1972 (Act No 54 of 1972).
- Genetically Modified Organisms Act, 1997 (Act No. 15 of 1997)
- Hazardous Substances Act, 1973 (Act No. 15 of 1973).
- Occupational Health and Safety Act, 1993 (Act No. 85 of 1993).
- Meat Safety Act, 2000 (Act No. 40 of 2000)
- Environmental Conservation Act, 1989 (Act No. 73 of 1989).
- National Environmental Management Act, 1998 (Act No. 107 of 1998).
- The Standards Act, 1993 (Act No. 29 of 1993).

2. SCOPE

The scope of this guideline is basic minimum data requirements that must be provided for all Stock Remedies submitted for registration under Act 36/1947 as new registration submissions, any proposed amendments or any other applications that require data submission and evaluation.

Applications for registration must include technical scientific data to support quality, safety and efficacy of the product/s.

Dossier/ Data Package Overview

A. General Information.
B. Pharmaceutical and Analytical Data.
C. Pre-Clinical Data.
D. Safety Data.
E. Efficacy Data.
F. Residue Data in relation to food producing animals.

For each part or section listed above, summarised details will be provided to guide applicants in compiling an acceptable dossier.

FOR MORE DETAILED INFORMATION, PLEASE REFER TO THE RELEVANT GUIDELINES ON THE WEBSITE OR OTHER INTERNATIONALLY ACCEPTED GUIDELINES.

Format of Submission of Documents

1. **Application forms**

All application forms must be **completed in full** for each new application, amendment, transfer, identical registrations (daughters and parallels). "Daughter" registrations may refer to the "mother" registration, but a sworn affidavit must be provided to verify particulars.

2 copies of the application form are requested, with at least one original signature.

Each page must be initialled at the bottom and signed on the last page. Sections 11 – 14 are often marked incorrectly or not completed – these are important sections as this information is required for other legislation (see other related Acts listed above).

A designated person must be appointed, in writing, by the company/legal entity to sign documents on their behalf in the registration process.

Please note that the application form is a legal document in terms of Act No. 36 of 1947.

A covering letter must accompany the application form and must detail the process that the applicant is requesting.

Proof of payment must accompany the application. Banking details are available from administrative staff.

Fees are amended on an annual basis and published in the Government Gazette.

2. **Labelling and package inserts**

2 copies of all labelling, including package insert must be supplied with the application forms. Labelling must be submitted in English only. Other languages cannot be approved by this office.

Please refer to the Labelling Guidelines for Stock Remedies for layout and content.

3. **Data dossiers**

Data dossiers must be submitted according to the relevant sections as described in the Data Requirements.

The dossiers must preferably be divided into each section and identified on the outer title page, e.g. Volume 1 of 4: A: General Information, etc. Name of product and company must be detailed.

A full table of contents for the entire dossier must be provided and correlate with page numbering. If the index and page numbering of an international dossier is sequential, insert this index and page numbering – this does not have to be re-done.

The data must be presented in **a bound format** that is easy to reference and store.

VERY IMPORTANT:

DO NOT SUBMIT DOSSIERS IN LEVER ARCH OR RING BINDER FILES: these break if dropped, pages go missing, and are cumbersome to work with and extremely difficult and bulky to store.

ELECTRONIC DOSSIERS MAY ALSO BE SUBMITTED: Please ensure that covering letter, application forms and labelling are submitted as **hard copies** to administration, but are also included electronically, if possible.

APPENDICES AND ANNEXURES IN DOSSIERS MUST BE KEPT TO A MINIMUM: please insert the information that is frequently included in such appendices/annexures under the relevant section of the dossier, e.g. specifications, certificates of analysis, results of tests, etc**. This is very tedious for evaluators this requires paging back and forth, wasting unnecessary time.**

Subsections of the various sections of the dossier must be delineated with tabs to identify the subsection e.g. Part B.1 API, etc.

Applicants are permitted to request exemption from sections if valid – motivation and justification must be inserted under this section to explain, with scientific reasons, why this section is not relevant or applicable to this dossier.

DO NOT SUBMIT DOSSIERS THAT YOU KNOW TO BE SUB-STANDARD – IT WILL DELAY THE REGISTRATION PROCESS. CHECK DOSSIERS DONE BY STAFF OR CONSULTANTS BEFORE SUBMISSION.

DATA REQUIREMENTS FOR STOCK REMEDIES

A. GENERAL INFORMATION

IMPORTANT: Table of Contents/Index for **whole** dossier must be submitted. (Each **section** must also have an Index.)

Data must be **bound** and **not** submitted in lever arch or ring binder files which bend and break. They are also heavy and bulky and utilise unnecessary space for storage.

1. Purpose of application.
2. Justification of the new product/new use/new dosage form etc.
3. Product summary.
4. Foreign registrations: a complete and translated, where applicable, status of licensing, registration, etc. including whether registrations have been refused or withdrawn, with reasons, must be included.
5. Certificates of registration/licensing, etc. (e.g. Australia, USA, EU, Canada, UK, New Zealand) must be included, and translated (by certified translator) if in any language other than English.
6. Approved international package insert/complete label text in English (e.g. Australian, USA, EU, Canadian, UK, New Zealand) must be submitted. If there is no English international label a translated (by certified translator) package insert/complete label is required.
7. Proposed referenced South African package insert must be submitted.
8. Exemption letters from the MCC's Scheduling Committee (if relevant) should be included in this section.
9. In the case of products containing genetically modified organism(s), an approval for the use of those ingredients must be obtained from the **Directorate: Genetic Resources** of DAFF. **This is done by the applicant**.
10. In the case of products claiming treatment, prevention or control of Notifiable or Controlled Diseases, an approval for the use of the product must be obtained from the **Directorate: Animal Health** of DAFF. **This is referred by our office**.

B. PHARMACEUTICAL DATA

(This is a summarised version for ease of reference – Pharmaceutical and Analytical, as well as Stability Guidelines MUST be referred to for details that must be submitted in the dossier).

1. Active Pharmaceutical Ingredient:

1. INN name/Chemical Names/CAS Approved/Internationally recognized name/Common names/ synonyms.
2. Empirical formula.
3. Molecular weight.
4. Occurrence of isomers and polymorphism where applicable.
5. Structure elucidation if New Chemical Entity.
6. Possible impurities and degradation products (describe).
7. Basic physical and chemical properties.
8. Specifications/standards of active pharmaceutical ingredient (API) – referenced pharmacopoeial specifications must be provided. If non-pharmacopoeial (usually in-house specifications) are given, the reasons for using these specifications must be scientifically substantiated and justified. This must be accompanied by a detailed description of analysis method/s and validation reports of analysis methods.
9. Certificates of analysis – minimum 2 recent batches (on valid letterhead of manufacturer, with date and signature of Quality Assurance Manager).
10. Source of active: name, address and site must be provided.
    GMP certification must be provided. Alternatively a CEP or accreditation by other aligned regulatory authorities or by a recognised GMP auditor may be provided. **These must be up to date and any conditions must be complied with**.
    If multiple sources:
    - Comparative critical tests e.g. Identification, assay, solubility, particle size, optical rotation, residual solvents and impurity profiles, performed on samples from each source to demonstrate physical and chemical equivalence, must be performed by the same laboratory (either the laboratory of the manufacturer or an independent laboratory). The same analytical methods and equipment must be used for these tests. These results must be presented in tabulated format.
    - A CEP (certificate of suitability) issued by an internationally acceptable regulatory body (e.g. EDQM) may also be presented, if available. Conditions must be adhered to must be maintained, and the CEP be updated according to date stipulated.
    - The API manufacturer must also submit the open section of the DMF (Drug Master File) available, which can be provided **if a CEP has not been issued**.
11. Stability data of the active pharmaceutical ingredient(s):

This must be provided by the manufacturer with method, time points for testing and tests performed, as in the specifications. A re-test date is the applied.

All specifications should be at the level of the latest editions of recognised pharmacopoeial references and monographs or other internationally accepted manuals and departure from such sources must be fully substantiated (e.g. in-house specifications). CoAs or MSDSs are NOT specifications.

2. Formulation:

Product details relating to the formulation and composition thereof must be supplied:

1. Trade name/ Registered name.
2. **Dosage form** e.g. powder, suspension, injectable, etc. and **route of administration** e.g. oral, injectable, topical, etc.
3. **Diluents for freeze dried formulations** must be fully described on the application form and in the dossier.
4. **Target species**.
5. Formulation composition in tabular format, expressed **for bulk (if applicable) and unit formula** (per unit is per tablet/capsule, per ml, per litre, per gram, per kg, per syringe, etc.) and must correspond to name, units and amount given in the application form.
6. Detail the **purpose** of each ingredient in the formulation
7. **Manufacturing formula** must be fully described (indicate whether raw ingredients are used **in** the formulation or used in order to manufacture the formulation). If potency adjustment is required (not allowed to exceed 5%), this must be stated on the application form (under Composition) and describe how this is to be done and how this may impact on the excipients.
8. The Animal Health Directorate of the Department of Agriculture must be consulted in the case of stock remedies containing imported ingredients of animal origin in terms of the Animal Diseases Act No. 35 of 1984 – certificates of origin and confirmation of TSE/BSE free status will be required in these cases. Veterinary vaccines must also be screened if new strains, uses, administration, etc. are envisaged.
9. The Genetic Resources Directorate of the Department of Agriculture must be consulted whenever any form of genetic related methodology has been used in the manufacture of the vaccine.
10. The Plant Health Directorate of the Department of Agriculture should be consulted in the case of stock remedies containing imported ingredients of plant origin where relevant. Advice can be given by the Directorate regarding such ingredients.

3. Raw material specifications and control procedures:

1. Specifications/standards and limits of inactive and other raw material (referenced pharmacopoeial or if non-pharmacopoeial must be substantiated), plus validation

reports of analysis methods and description of analysis methods and control procedures of inactives must be fully described.

2. Purpose of each inactive (e.g. emulsifier).
3. Identification of inactive and other raw material irrespective of whether CoA is supplied by supplier must be performed.
4. Water testing procedures and results, where applicable.

4. Container and packaging specifications:

1. Full details of immediate container material/s and size/s, method of closure, applicator and administration set, or any other relevant container details must be fully described (also on application form). Specifications and limits must be provided regarding the nature of the material, dimensions, closure systems and any other relevant details, especially with regards to immediate container.
2. Details of the manufacturer of containers, etc. must be provided.
3. Filling process of the immediate container with formulation (if not described under manufacturing procedures).
4. Briefly describe any outer container/secondary container (also detail on application form).
5. Provide details of primary and secondary packers, if relevant (also detail on application form).
6. **Include all pack sizes** (also detail on application form).

5. Manufacturing procedures (including flow diagram)

1. Manufacturing facility/ies and physical address/es (including packers).
2. The entire manufacturing process (*including* flow chart) including all materials, processes and manufacturing method, **plus quality control (in-process and terminal control procedures).**
3. The filling process of the immediate container must be described in detail. Where sterility is part of the process, this must be monitored and processes detailed.
4. Batch formula and batch size must be given.
5. The Quality Assurance manager must be identified, and signed, dated copies of QC procedures must be provided.
6. A copy of GMP (Good Manufacturing Practice) certificate or similar accreditation, if relevant, must be supplied.

6. Finished product:

1. Final/finished product and batch release specifications must be clearly detailed.
2. QC involving details of final/finished product (batch release documentation) must be provided for at least 2 production or pilot batches.

3. Certificate of analysis (at least 2 batches) on company letterhead, dated and batch release documentation signed by QA manager.

7. Stability data (3 batches):

Stability data must be presented as required in the Stability Guidelines for Stock remedies.

The stability data required in this section will be the stability of the formulated finished product in the proposed immediate container (size, material and type – as applied for).

The shelf life will be proposed by the applicant according to the results obtained.

In summary, the stability studies must be provided as follows:

a. Stability study protocol (summarised overview of study) must include parameters measured:

- Confirmation that the formulation and immediate container (size and material) of the product to undergo stability testing is the formulation and immediate container as applied for.
- All tests (**with specifications fully described**) for example: assays or titres and any relevant tests (such as appearance, moisture content, degradation products (if applicable), sterility, appearance, pH (where applicable), certain contaminants, safety tests, etc**.) in line with specifications.**
- Time points must be clearly detailed and identify which tests are done at each time point. Time intervals between testing will be every 3 months for the first year, every 6 months over the second year and annually thereafter until conclusion of the study when the final testing is done.
- Immediate container (size/s, material/s, type) must be confirmed and this information corresponds to the particulars in the application.
- Temperature/s and relative humidity, Accelerated studies may be submitted as well as real time studies. The following table confirms minimum testing times and conditions for products to be submitted:

	Storage conditions	Minimum time period at submission
Long-term testing	25 ± 2 ^{o}C / 60 ± 5 % RH	9 months
Intermediate	30 ± 2 ^{o}C/ 65 % ± 5 % RH	6 months if significant change at accelerated
Accelerated	40 ± 2 ^{o}C / 75 ± 5 % RH	3 months

Where "significant change" occurs due to accelerated testing, long-term data for a period longer than nine months may be required to justify a provisional shelf-life of 24 months. "Significant change" at accelerated testing conditions is defined as:

a) A 5 % potency loss from the initial assay value of a batch;
b) Any specified degradant exceeding its specification limit;
c) The product exceeding its pH limits;
d) Failure to meet specifications for appearance and physical properties, e.g. colour, phase separation, suspension details, delivery per actuation, caking, hardness.

- Batches tested must be identified.

b. Results for each batch, in tabular format, listed as follows:

- Rows for specifications, assays, all other tests and relevant information.
- Columns will be the time points and results obtained for each time point. Note: Not all parameters have to be tested at each time point but must be recorded at the relevant time point. Certain parameters are essential for day 0 and proposed end point of stability.

All certificates of analysis must be provided for each batch **(actual descriptions/values must be given – not terms such as "complies" or "satisfactory")** and dates must correlate with the time period that the stability study is being conducted. All CoA's must be on a letterhead and dated and signed by the designated QA manager of the laboratory.

Method/s of analysis must also be provided with validation of method/s.

c. Conclusion – this must include the motivation and discussion for the proposed shelf life (for veterinary biologicals the shelf life will be 3 months less than time tested e.g. 27 months testing will give a shelf life of 24 months). A commitment to submit ongoing data must also be supplied where accelerated studies have been done and a provisional shelf life is motivated.

8. Analysis:

Analytical data must be submitted in detail according to the Pharmaceutical and Analytical Guidelines for Stock Remedies.

All analyses must be conducted by an accredited analytical laboratory with details of standards used for analysis results, validation of methods used and records to verify this. If a non-accredited laboratory (not recommended) is to be used, please consult with the relevant Technical Advisor for Stock Remedies regarding possible risks involved with this.

9. Pharmaceutical development:

In the pharmaceutical development of a product for a new chemical entity, this section can be used to describe the discovery of the product for the intended use and how it was developed into a product that would have the properties claimed.

For generic products, applicants may also describe the product but details of the development are not necessary.

C. PRE-CLINICAL DATA

Pre-clinical data is required for New Chemical Entities (NCEs) or in cases where Maximum Residue Limits have not been established for an API.

Please either request exemption for submitting the entire pre-clinical data package in cases where API's are well known, with necessary scientific justification and motivation, or submit data as follows.

- **Pharmacological/Metabolic data must include where relevant:**
  - Pharmacodynamics of chemical group
  - Pharmacodynamics of active ingredient
  - In vitro studies for efficacy e.g. efficacy against certain parasites, minimum inhibitory concentration for antimicrobials,
  - Pharmacokinetics of substance in animals (including target species), including various routes of administration.
  - Dose determination trials/ minimum effective concentration or dose/ justification for combinations of substances, e.g. synergistic effect, etc.
  - Dissolution studies (if applicable)

- **Mammalian toxicity studies:** The applicant is referred to the VICH guidelines or MCC/SAHPRA guidelines entitled **"Guideline on pre-clinical safety studies for veterinary medicines" (www.sahpra.com)**
  - In the case of a generic product, this data should be summarised, with appropriate references (preferably tabular format).
- **Environmental Risk Assessment Studies or literature must also be submitted. Applicants can also refer to VICH Guidelines.**

CLINICAL SECTIONS OF DOSSIER:

IMPORTANT: All trials must be conducted according to Good Clinical Practice (GCP) For all locally conducted clinical trials, all trial protocols must be submitted to the technical advisor for approval.

D. SAFETY DATA

A table of contents for this section must be inserted.

A safety data trial summary in tabular format must be inserted in the beginning of the section.

For all laboratory and clinical safety trials, please refer to VICH guidelines. Development of the DAFF guidelines is in process.

All trials must be conducted according to GCP.

Data from other internationally recognised countries may be submitted, if relevant and conducted according to GCP and safety guidelines applicable in that region.

E. EFFICACY DATA

A table of contents for this section must be inserted

An efficacy data trial summary in tabular format must be inserted in the beginning of the section.

IMPORTANT: All trials must be conducted according to GCP.

Animal Ethics Committee approval – must be an independent, impartial committee with at least one member of NSPCA present, one member must be from DAFF: Animal Health Directorate and the committee must be independently selected with DAFF inputs (i.e. not selected by company concerned).

Comparative (comparing new generic with innovator product) efficacy trials (generics) and full efficacy trials (new chemical entities) are required in South Africa in herbivores for anthelmintics, endectocides and in all target species for ectoparasiticides/endectocides.

Data may be submitted from other countries in support of data generated in South Africa (only if relevant).

In the case of any antimicrobial product, any applications will have to be reviewed by the Antimicrobial Working Group. Only therapeutic claims for specific conditions will be allowed, i.e. no growth promotion claims will be allowed on labelling, package insert or advertising.

NO CLAIMS AGAINST RESISTANT STRAINS OF ANY PARASITE OR MICROBE WILL BE ALLOWED.

F. RESIDUES

A table of contents for this section must be inserted.

A residue trial summary in tabular format must be inserted in the beginning of the section.

All trials must be conducted according to GCP.

Data important for calculation of withdrawal periods include:

Theoretical Maximum Daily Intake (TMDI)

Acceptable Daily Intake (ADI)

No Effect Level (NOEL)/ No Adverse Effect Level (NOAEL) and

Acute reference dose (ARfD)

Data to support proposed MRLs must be submitted and motivated.

For the evaluation of residue data where no international MRLs have been determined, the applicant must submit the Maximum Residue Limits (MRL) determined by Directorate: Food Control, Department of Health, published in the Foodstuffs, Cosmetics and Disinfectants Act, 1972 (Act No. 54 of 1972) if available***** or propose MRLs calculated by a known recognised toxicologist that will provide a risk evaluation report to submit to Directorate: Food Control, via the Registrar's office.

Tissue depletion residue studies for each major food producing species must be submitted.

Analytical methods must be provided.

Validation of methods must be provided.

If MRLs have not been determined, please note the following:

- Suitable GCP residue trials conducted in other countries will be acceptable, if motivated and justified.
- Extrapolation of results to a different food producing animal species will NOT be permitted (e.g. cattle to sheep, sheep to goats, chickens to ostriches, etc.)

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*** The Department of Health determines MRL's for chemical entities to be used in FPA. Use of MRLs determined by internationally recognised regulatory authorities (e.g. CODEX and JECFA, EMEA, USA, APVMA, New Zealand), may be allowed if relevant species/tissue MRLs are available for the particular active ingredient and metabolites. This must be suitably motivated and justified.**

The Toxicological Risk Assessment Requirements and currently published MRLs may be obtained from DoH: Directorate Food Control (Foodstuffs, Cosmetics and Disinfectants Act, 1972 (Act No. 54 of 1972).

4. CONCLUSION

As previously stated, specific guidelines regarding different types of dossiers or sections of the dossier are available on the website.

Use of internationally accepted guidelines is also acceptable and the use of the VICH guidelines is encouraged.

REFERENCES:

Applicants are at liberty to use the following guidelines for registration purposes

Act No. 36 of 1947: Stock Remedy Regulations R956 of September 2006: Annexure C – Data Requirements.

SAHPRA (replacing MCC): guidelines may be referred to.

VICH: all guidelines may be referred to.

WAAVP: endo- and ectoparasites in conjunction with technical advisor for local trials.

APVMA: guidelines may be referred to.

MCC/SAHPRA: guidelines may be referred to.

EMA: Veterinary medicines and biologicals. Guidelines may be referred to.

USA: FDA and USDA/APHIS: Guidelines may be referred to.

NEW ZEALAND: Guidelines for residues in food producing animals, data requirements for residue trials and MRL's may be referred to.

OIE and FAO Manuals may be referred to where applicable.