AGRICULTURAL REMEDIES REGISTRATION REQUIREMENTS AND PROCEDURE DOCUMENT

1999

Registrar: Act No. 36 of 1947
Private Bag X343
Pretoria 0001

The Republic of South Africa
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1. INTRODUCTION

The registration of an agricultural remedy involves a number of actions. While every effort will be made to expedite the review of an application, the applicant should allow a reasonable length of time for the review.

A well-prepared application will be easier to process and will be processed faster than in the case of a poorly prepared submission. Special attention has to be paid to the presentation of efficacy and residue data. **Only data which has a direct bearing on the registration application should be presented**. The identity of all coded compounds must be indicated.

Industry is encouraged to develop and register formulations that are less hazardous and where the problem of container disposal is addressed. These include micro-encapsulated formulations, water dispersible granules, water soluble sachets, tablets and biotechnology products. Cognisance should also be taken of the "International Code of Conduct on the Distribution and use of Pesticides" and "Guidelines for the Registration and Control of Pesticides" issued by the Food and Agriculture Organisation of the United Nations (FAO), as well as the "GCPF Position Paper on Intellectual Property" issued by the Global Crop Protection Federation.

This document must be read together with the Fertilizers, Farm Feeds, Agricultural Remedies and Stock Remedies Act, 1947 (Act No.36 of 1947) (hereafter referred to as Act 36 of 1947) and the Regulations promulgated under this act.

2. REGISTRATION REQUIREMENTS

Any application for the registration of an agricultural remedy or the renewal thereof shall be submitted to the Registrar, Act No. 36 of 1947, Private Bag X343, Pretoria 0001.

An application for registration or application for an amendment of an existing registration shall be submitted on application form - Application for the Registration of an Agricultural Remedy*. This form is obtainable from the office of the Registrar, telephone (012) 319 7187 or the web-site: www.nda.agric.za/act36/main.htm

The application form and the proposed label shall be submitted in triplicate. Lists I and II need only be submitted in single-fold. It is expected of the applicant to complete each applicable paragraph in full, every time he submits an application form. The application must be accompanied by the prescribed application fee which is indicated on the web-site. All cheques must be made out in favour of the Director General - Agriculture. For the renewal of an existing registration see 2.6.

* The application form also includes List I (Active Ingredient Dossier) and List II (Formulated Product Dossier)

The regulations require that prior to the commencement of any trials the Registrar must be informed in writing of the intention to conduct such trials in order that he may inspect their performance. Furthermore, the Act makes provision for the Registrar to call for any further information in order to determine whether the remedy is acceptable in the context of public interest, suitability and biological efficacy.

2.1 Registration of an agricultural remedy containing a new active ingredient.

The following are required:

2.1.1 Covering letter clearly stating the purpose of the application and a brief description of all submitted documents.

2.1.2 Application form fully completed in triplicate.

2.1.3 List I and List II fully completed with relevant information and supporting documents in single fold.

2.1.4 A copy of the laboratory report on the Physical and physico-chemical properties of the formulation as outlined in “Manual On The Development And Use Of FAO Specifications For Plant Protection Products. March 2006 revision of the first edition.” only available on the FAO website:- www.fao.org

2.1.5 MSDS- material safety data sheet compiled according the SABS 16 point proposal in single fold. The MSDS must have the details of the Registration Holder as registered in South Africa on it.

2.1.6 The prescribed application fee.

2.1.7 Proposed label in triplicate. The label has to conform to the requirements of the "Guidelines for the RSA Classification Code of Agricultural and Stock Remedies and Associated Labeling Practices" and relevant regulations.

Where the remedy will also be marketed in a small pack for the home-garden market the proposed home-garden label (which obviously will differ from the agricultural label in respect of indications regarding dilution, method of application and often pests, diseases or undesirable plants controlled) should also be submitted.

2.1.8 A single copy of the pharmacology, toxicology and environmental impact studies of the active ingredient(s) as well as toxic metabolites. The data from reputable laboratories conforming to GLP (good agricultural practice) are acceptable.

2.1.9 A single copy of the formulation toxicity data (optional for hazard classification).

2.1.10 A single copy of the experimental data on the biological efficacy and where applicable phytotoxicity and residues on the commodity concerned under South African conditions. Guidelines regarding experimentation to determine efficacy and phytotoxicity are in some cases available from the Registrar's office. If guidelines are not available the relevant Technical Adviser should be consulted in order to establish the requirements.

2.1.11 Requirements regarding residue determination are set out in the Residue Policy Document.

2.2 Registration of an agricultural remedy where the active ingredient and formulation are identical to a registered product. (Commonly referred to as daughter or parallel registrations)

The following are required:

2.2.1 Refer to 2.1.1 -2.1.7 (for both daughter and parallel registrations)

2.2.2 Contract/agreement between parties involved in the format recommended by the Registrar's office. (only for daughter registrations)

2.3 Registration of an agricultural remedy where the formulation has changed from that of a registered product. This includes changes in the formulation type or change in the concentration of active ingredients

The following are required:

2.3.1 Refer to 2.1.1 -2.1.7

2.3.2 A letter from the manufacturer of the technical material stating that the applicant will be supplied with the technical material or formulated product

2.3.3 A single copy of the formulation toxicity data (optional for hazard classification). See 3.6.

2.3.4 Efficacy, and where applicable, phytotoxicity data on various known sensitive cultivars in which the candidate remedy has been compared to a similar remedy (formulation) on a commodity or commodities on which it is used extensively. Depending on the number of registered claims for that particular remedy (formulation) trials will have to be undertaken on at least one to four different commodities. As a general rule the product has to be tested on 30 percent of the

end-uses on the label for non- systemic remedies and 40 percent of end-uses for systemic remedies. Three trials on each crop/pest combination are required.

2.3.5 Where applicable, results of residue analyses on the commodities on which efficacy data were undertaken at the termination of the official withholding period. These must include the most important crops as well as any relevant export crops. See also 2.1.10

2.3.6 Should the company be using a source for technical material that was not used by the company before, then 2.4 below also applies to the application.

2.4 Registration of an agricultural remedy containing a generic active ingredient where the source of the active ingredient is not identical to that of the registered product.

The following are required:

2.4.1 Refer to 2.1.1 -2.1.7

2.4.2 A letter from the manufacturer of the technical material stating that the applicant will be supplied with the technical material or formulated product containing the technical material.

2.4.3 Full details on the identity and purity of the technical material. Information must be submitted on the identity and quantities of impurities present in the technical material. If FAO specifications are available, the technical material must conform to FAO specifications.

2.4.4 The information required in 2.4.3 must be substantiated by analytical data, preferably from an independent, accredited laboratory for a five batch analysis. See also the "Guidelines on Equivalence of Agricultural Remedies (Pesticides)" and “Minimum data requirements for approval of an alternative source of the technical grade active ingredient (TGAI) of a pesticide” for more details obtainable on the NDA web-site.

2.4.5 Since deviations from the original active ingredient's specifications may result in the toxicity data generated to support the original registration no longer being applicable to the generic active ingredient, new toxicity data may have to be submitted.

2.4.6 Applicants wishing to register products with generic active ingredients are advised to subject their technical material to the above tests before the commencing of field trials.

2.4.7 A single copy of the formulation toxicity data (optional for hazard classification). See 3.5.

2.4.8 Experimental efficacy, and where applicable, phytotoxicity data as specified in 2.3.4

2.4.9 Where applicable, results of residue analyses as specified in 2.3.5

2.5 Amendments to existing registrations.

In the case of an amendment the following are required:

2.5.1 Application form fully completed in triplicate.

2.5.2 The prescribed application fee.

2.5.3 The full label including, if applicable, the proposed amendments (additional claims, altered recommendation, etc.) in triplicate. The label has to conform to the requirements of the "Guidelines for the RSA Classification Code of Agricultural and Stock Remedies and Associated Labeling Practices" and relevant regulations.

2.5.4 In the case of a proposed new end-use a single copy of the experimental data on the biological efficacy and where applicable phytotoxicity and residues.

2.5.5 In the case of an amendment of the formulation,
Formulations changes can be regarded as significant or minor changes. In the case of a significant change (change in formulation type or concentration of active ingredient) refer to 2.3 above. A minor change includes request by the Registrar or initiatives by the industry to use safer inerts, or alternative inerts in the formulations. Phytotoxicity trials on various known sensitive cultivars in which the candidate formulation was compared to the old formulation on a commodity or commodities on which it is used extensively.

2.5.6 If the registration holder obtains he active ingredient from a new source other than that originally registered no efficacy data will be necessary provided that the formulation details stay the same. Full details on the identity and purity of the technical material as requested in 2.4.4 and 2.4.5 must be submitted.

2.6 Renewal of registration.

All registrations will be valid for a three year cycle and must be renewed after three years, from date of registration. An application for renewal has to be made on the appropriate application form and be accompanied by the prescribed application fee.

The following are required when applying for renewal:

2.6.1 Renewal form fully completed in triplicate.

2.6.2 The prescribed application fee.

2.6.3 The Registrar may request that copies of the printed label be submitted. .

2.6.4 If the particular remedy is not marketed at all, typed copies of the approved label may be submitted.

2.6.5 If the label is printed directly onto the container or is too large (e.g. 50 kg bag), legible photocopies may be submitted (maximum A4 size).

2.7 Registration of minor use remedies. (Refer to Annexure II)

Minor uses of agricultural remedies are defined as those desired uses of registered agricultural remedies for which the anticipated increase in the volume of sales is not sufficient to persuade the manufacturer or registration holder to carry out the research required for registration. Generally these will have no registered remedies or if they do have they would have been developed using the minor use procedure

2.7.1 If residues are likely to be present at harvesting, local residue data must be submitted.

2.7.2 The requirements for efficacy must be discussed on a case by case basis with the Registrar and the applicable Technical Adviser

2.7.3 All other requirements for registration must be provided depending on which one of the categories under section 2.1 -2.5 the application falls within.

2.8 Generic compounds exempt from efficacy data.

In the case of the following active ingredients no experimental or efficacy data needs to be submitted. This does not, however, exempt these active ingredients from being evaluated for chemical equivalence as laid down in 2.4.4 and 2.4.5. These compounds are "general knowledge" products which have been in use for many years and should not be subjected to sophisticated assessment protocols for **current uses i**f they meet the necessary specifications. If new formulations are developed, or dosages changed, efficacy and/or phytotoxicity data may be required.

Aluminium phosphide
Arsenic/chromium/copper
Borax/PCP
Bordeaux mixture
Boric acid
Calcium arsenate
Calcium hypochlorite
Captab
Copper oxychloride
Copper sulphate
Creosote
Creosote/coal tar
Didecyl dimethyl ammonium chloride (except for Post harvest treatments)
EDB
Gamma-BHC/TBTO
Magnesium chlorate
Magnesium phosphide
Metaldehyde
Metam-sodium
Methyl bromide
Mineral Oil
N-alkyl dimethyl benzyl ammonium chloride
Naphthalene
PCP
PCP/zinc naphthanate
Poly(2-hydroxyethylene-dimethyliminio-2-hydroxypropylene-dimethyliminio-methylene) dichloride
Sodium hypochlorite
Sulfur
Tartar emetic
Trichloroisocyanuric acid
Zinc phosphide

2.9 Emergency Registrations

Priority will only be given to applications which are of national importance and cases where there are no existing registrations available or where existing registrations are only partially effective. Requests for the priority treatment of applications have to be well motivated and enjoy the support of recognised organisations, e.g., the Agricultural Research Council, grower organisations, provincial departments of agriculture, conservation bodies etc. If there are data gaps (efficacy and residue), the registration may be granted conditionally, provided the outstanding data is submitted within a reasonable time.

Requirements are as per others depending on which category the registration falls under.

2.10 Import Permits

Import permits for agricultural remedies are only granted for the purpose of generating data through trials for registration purposes. The following information must be submitted

2.10.1 Description of the agricultural remedy - this should include the active ingredient content and type of formulation

2.10.2 Intended use of Agricultural Remedy -

2.10.3 Quantity to be imported

2.10.4 Port of entry

2.10.5.1 Trial protocol and site of trials . Sufficient detail should be given to estimate the amount of product that will be needed per trial.

2.10.6 Country of Origin and registration status in Country of Origin

210.7 The prescribed fee

2.11 Advertisements

All advertising or promotional material related to Agricultural Remedies must be submitted to the Registrar's office for approval prior to publication or broadcasting. Advertisements are checked for technical accuracy according to the applicable registered products. Advertisements approved may still be subjected to the Regulations of the Advertising Standards Authority of South Africa.

The following must be submitted for approval

2.11.1 Advertisement in triplicate, accompanied by a covering letter

2.11.2 The prescribed fee

2.12 Certificate of Free Sale

2.12.1 The request for Certificate of Free Sale by the registration holder must be submitted in writing to the administration offices of the Registrar. The company must supply the registered trade name and registration number of the product (s) .These must correspond with the registration certificate that was issued when the product was registered.

2.12.2 The prescribed fee

2.13 Registration of Biological Agricultural remedies

Registration of biological products are treated in the same manner as the registration of chemical compounds except for the following

2.13.1 In the case of a living organisms – in addition to the requirements of Act No 36 of 1947 the applicant is required to get a permit from the Directorate :Plant Health to bring the product into the country

2.13.2 Generally speaking for biological control agents residue is not required. However sometimes due to the biological nature of the agent – by-products may be produced which are of toxicological significance. In such cases residue data may be required.

2.13.3 Botanical extracts - residue data is always required unless exempted by the Department of Health.

2.13.4 Generic registrations for biological products cannot be considered. Due to the nature of these products, all applicants must prove the Toxicology, efficacy and physical and chemical properties of their products. (Biological products maybe influenced by the strain, site of isolation, conditions under which produced etc)

3. TOXICOLOGICAL REQUIREMENTS

Before an agricultural remedy containing a new active ingredient may be registered in South Africa, approval must first be obtained from the Department of Health. Approval can be obtained in various ways as indicated in 3.1, 3.2, and 3.3. In the case of microbial pest control agents please refer to the "Guidelines for the toxicological evaluation of microbial pest control agents".

Please note that toxicology, ecotoxicology and residue data must be generated under GLP. A copy of the GLP certificate must be submitted. In the case of residue data the analysis of residues must be done by a GLP accredited Laboratory

3.1 Evaluation by the Department of Health.

3.1.1 The applicant submits an application for registration and all relevant documentation (including the full toxicological package) to the Registrar.

3.1.2 The Technical Adviser requests the Department of Health in writing to evaluate the toxicology of the new active ingredient. The application form, draft label, residue data, Material Safety Data Sheet (MSDS), specifications and toxicological data are then forwarded to the Department of Health.

3.1.3 The Department of Health evaluates the data and prepares a risk assessment using human health and environmental safety criteria. If the risk assessment is favourable, permission is then given to the Department of Agriculture to proceed with the registration.

3.1.4 The Technical Adviser evaluates the registration application and makes a recommendation to the Registrar.

3.2 Toxicology and other data required for new active ingredients

Refer to the Department of Health's website: www.doh.gov.za

3.4 Toxicity data required for certain generic active ingredients.

A formulation containing a generic active ingredient may be registered without the submission of extensive toxicology data provided it does not differ significantly in degree of purity or nature of impurities from the composition registered in the dossier accompanying the original application for the active ingredient.
After studying the analytical data referred to in 2.4.3, the Registrar may, however, determine that the technical material of a generic active ingredient is not chemically equivalent to the originally approved technical material. In such a case, at least the following will be required:

* Manufacturer of active ingredients. Documentary proof should be supplied.
* Formulation details
* The spectra and identity of all impurities (if present)
* Analytical and statistical methods – an analysis of the technical material by means of recognised analytical techniques, e.g. gas chromatograph
* A comparison with an analytical standard
* Confirmation of the identity of the technical material on ~~a~~ e.g. a mass spectrometer
* A comparison with a standard from a library
* Terminal residues (where applicable)
* Acute toxicity
  - Oral LD_{50} - rat or mouse
  - Dermal LD_{50} - rat or rabbit

Inhalation LC_{50} - rat
Skin sensitisation - guinea pig
Primary dermal irritation/corrosion - guinea pig
Primary eye irritation/corrosion

Depending on the composition of the technical material, the Registrar or Department of Health may request further toxicological data in addition to the above.

3.5 Toxicity data required for new formulations

The submission of formulation toxicity data is optional, however, it is needed in some cases for establishment of a hazard classification (see "Guidelines for the RSA Classification Code of Agricultural and Stock remedies and Associated Labelling Practices"). The following may be required:

* Acute toxicity
Oral LD_{50} - rat or mouse
Dermal LD_{50} - rat/rabbit
Inhalation LC_{50} - rat
Skin sensitisation - guinea pig
Primary dermal irritation/corrosion - guinea pig
Primary eye irritation/corrosion

3.6 Inert ingredients

Inert ingredients used in formulations must be toxicologically and environmentally acceptable.

3.7 Living modified organisms resulting from modern biotechnology.

3.7.1 Certain living modified organisms (LMOs) resulting from modern biotechnology will find their application in the field of plant protection and pest control. Although these LMOs are controlled by the Genetically Modified Organisms Act (Act 15 of 1997), some will also be controlled by Act No. 36 of 1947. These will include organisms genetically modified to express certain toxins. Excluded will be crops that have been genetically altered to be resistant to certain insect species, plant pathogens or herbicides as these will be controlled exclusively by the Genetically Modified Organisms Act.

3.7.2 No agricultural remedy derived from a recombinant DNA organism may be released (trial release and general release) unless a risk assessment to evaluate the risk

posed by the genetically modified organism to human health and the environment has been carried out and the necessary permits have been obtained. An evaluation of the risk to the environment should cover all issues required by the Environmental Impact Reports in terms of the Environmental Conservation Act. The risk assessment should be done by a biological safety committee appointed by the organisation concerned. SAGENE is available to provide advice when required. Cognisance should also be taken of the United Nations Environment Programme (UNEP) Technical Guidelines on Safety in Biotechnology.

3.7.3 Efficacy trials have to be conducted over at least two seasons.

3.7.4 A number of safety assessment parameters have to be taken into account. These are the following:

* Characteristics of the donor, recipient or (where appropriate) parental organism(s)
* Characteristics of the modified organism
* Health considerations
* Environmental considerations

Full details appear in the Genetically Modified Organisms Act (Act 15 of 1997). Contact the Director: Genetic Resource, Private Bag X973, Pretoria, 0001 for more information.

3.7.5 The registration package and all relevant documentation is submitted in the usual way to the Registrar. The same registration procedure as laid out in Chapter 4 applies.

4. REGISTRATION PROCEDURE

Upon receipt of an application for registration by the office of the Registrar the application is processed by means of a number of steps. These are the following:

4.1 The application is entered into the records of the office of the Registrar. A receipt is issued by the Directorate of Finance for the registration fee.

4.2 After obtaining the receipt the application and all relevant documentation are forwarded to the Technical Advisory Services.

4.3 In the case of a new active ingredient the Registrar's office will forward the toxicological dossier to the Department of Health together with a proposed maximum residue limit (where applicable).

4.4 If a risk assessment is not available the Department of Health prepares a risk assessment of the agricultural remedy, using human health and environmental safety criteria.

4.5 The Department of Health classifies the product according to the RSA Classification Code.

4.6 Efficacy data may be forwarded to relevant specialist research institutes for comments.

4.7 Upon receipt of the comments and/or the risk assessment Technical Advisory Services will proceed to process the application. If the Technical Adviser is satisfied that the remedy in question complies with all the requirements registration will be recommended.

4.8 All documents are indexed and filed.

4.9 The office of the Registrar, acting upon the recommendation of Technical Advisory Services, makes a final decision on the application. If the application is successful a registration number will be allocated and a registration certificate issued.

4.10 Under no circumstances will any information be given to any person that a registration application has been received by the Registrar or that such an application is under consideration. Once registration has been granted the agricultural remedy name, registration holder and purpose of registration (as per approved label) may become publicly available. However confidential information as per Registration application form remains confidential.

5. Binding and Presentation of Registration Dossiers

- Use two-ringed files of appropriate thickness (e.g. Lever Arch Files).
- The different part of the dossiers should be separated by flagged interleaves which have been clearly labeled e.g. APPLICATION FORM, MSDS, LABEL etc.
- Do not use plastic sleeves to separate documents.
- Do not staple documents.
- When more than one file is used, label them appropriately e.g. File 1 of 2 followed by trade name and company details.
- Toxicology data must be filed separately from the rest of the Dossier.

ANNEXURE 1

CHECKLIST FOR REGISTRATION APPLICATION DOSSIER FOR AGRICULTURAL REMEDIES

Note: All registration application should have the following information in order to facilitate the registration procedure

1. **Application fee**. All cheques to be written out in favour of the Director-General (Agriculture).

2. **Covering letter** clearly stating the purpose of the application and a brief description of all submitted documents.

   e.g.
   - New active ingredient
   - New formulation
   - New end use/claim
   - New source of Active Ingredients
   - Generic registration
     -Parallel registration (An alternative trade name within the same company of a registered product)
   - Daughter (Company A gives Company B permission to register and sell Company A's product under Company B's Trade name)
   - Label amendment

3. **Letter of Supply**, for submissions involving generic products, change of source of supply for active ingredient, transfers and daughter, a letter from the source of active ingredient, formulator of the product and original registration holder in case of daughter and parallel registrations are required.

4. **Contract** – in the case of Daughter Registrations – a copy of the contract that exists between the two parties must accompany the application

4. **Product Label**, three hard copies of a proposed draft label in English.

5. **Application Forms** (3 copies) are required for all submissions. Also, include List 1 and List II and supporting documents to Lists I and II too. All information and supporting documentation (certificate of registration in country of manufacture) requested on the application form must be submitted.

6. **Chemical and the Physical specifications** of the formulated product. = List II and supporting documentation

7. **Material Safety Data Sheet** of the formulated product in the name of the registration holder in South Africa.

8. **Chemical Equivalence** report on five Batch analysis. This must be submitted for all generic registrations and in cases where the source of the active ingredient has changed.

9. **Toxicological data** (where applicable).

10. **Residue data** (refer to residue trial data document).

11. **Efficacy data (**a minimum of 3 trials per crop/pest combinations done at 3 sites over 2seasons)

Compiled by the Technical Advisors (Agricultural Remedies - Act No. 36 of 1947).

ANNEXURE II

Procedure for a registration application to fall under "Minor use Registration".

This document has been drafted to clear up any confusion on how Act No 36 of 1947 currently handles "Minor Use Registrations"

Minor uses of agricultural remedies are defined as those desired uses of registered agricultural remedies for which the anticipated increase in the volume of sales is not sufficient to persuade the manufacturer or registration holder to carry out the research required for registration. This definition emphasizes that it is the projected increase in annual sales of the remedies that are minor, not necessarily the crop or pest.

If residues are likely to be present at harvest, local residue data have to be submitted.

A. Minor use registration will only be considered when :-

1. The toxicological evaluation of the active ingredient has already been evaluated by the Department of Health.
2. The registered formulation has proven it's efficacy for same disease/pest on other crops at the local level
3. If residues are applicable – that they have been conducted locally and conducted according to Act No. 36 of 1947's Guidelines

NB: Should the application not meet any of the above requirements, it will not be treated as a minor use application and full registration requirements apply

B. Submit a registration application with the following: (NB: A registration application must be submitted with the following attached to be considered by the Registrars Office)

1. Motivation as to why you think that the particular claim should be considered "minor" This should include the history of the crop and how previous registrations if any where considered. Letters of support from various grower associations will strengthen the motivation

2 Motivate why data can be extrapolated from other data. Include reports from Experts in the particular field. (Preferably more than one). Include scientific reports if available

4. Submit all other documents/data/ etc necessary for a complete registration dossier

Once the application has been received, the merits of application, will be evaluated by The Registrar and his Technical advisors. Should it be necessary external experts may be consulted to aid the evaluation.

The applicant of the "minor use" registration will be informed as to whether his application has been successful or not.