MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

GUIDELINE ON PRECLINCAL SAFETY STUDIES FOR VETERINARY MEDICINES

This guideline has been prepared to serve as a recommendation to applicants wishing to submit data for preclinical studies. It represents the Medicines Control Council's current thinking on this topic. It is not intended as an exclusive approach and does not bind the MCC nor confirm any rights for or on any person. Alternative approaches may be used but must be scientifically justified. The MCC is committed to ensure that all studies are conducted in line with good practice guidelines. The MCC make amendments in keeping with the knowledge which is current at the time of consideration of safety data

REGISTRAR OF MEDICINES
MS M. P. MATSOSO
DATE: 30-05-2003

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1. PRECLINICAL STUDIES

The safety documentation of the dossier shall show:

- the potential toxicity of the veterinary medicine and any dangerous effects which may occur under the proposed conditions of use in animals. These should be evaluated in relation to the severity of the pathological condition concerned;
- the potential harmful effects to man of residues of the veterinary medicine or substance in foodstuffs obtained from treated animals and what difficulties these residues may create in the industrial processing of foodstuff;
- the potential risks which may result from the exposure of human beings to the medicinal product, for example during manufacture, in feed mixing of or on administration to the animal;
- the potential risks for the environment resulting from the use of the medicinal product.

All results shall be reliable and valid generally. Where ever appropriate, mathematical and statistical procedures shall be used in designing the experimental methods and in evaluating the results. Additionally, clinicians shall be given information about the therapeutic potential of the product and about the hazards concerned with its use.

The following preclinical information must be submitted

i. Pharmacology
ii. Pharmacodynamics
iii. Pharmacokinetics
   a Kinetic and metabolism in rats
   b Kinetic and metabolism in primates)

1.1 Toxicity

The study procedures, as found in the latest published guidelines of the following authorities, are acceptable for Preclinical Studies to be performed:
OECD Guidelines for Testing of Chemicals and/or
EEC Directives, Methods for the Determination of Toxicity, and/or
US EPA Pesticide Assessment Guidelines, and/or
JAPAN/MAFF: Testing Guidelines For Toxicity Studies

1.2 Acute toxicity

1.3 LD_{50}

Single-dose toxicity studies can be used to:

- predict the possible effects of acute overdosing in the target species;
- predict the possible effects of accidental administration to humans;
- predict the doses which may usefully be employed in the repeat dose studies;
- assess the relative toxicity of the compound.

Single dose toxicity studies should reveal the acute toxic effects of the substances and the time course for their onset and remission.

These studies should normally be carried out in both sexes of at least two mammalian species. One species may be replaced, if appropriate, by an animal species for which the medicinal product is intended. Preferably two different routes of administration

should be studied. The route selected should be the same as that proposed for the target species. If substantial exposure of the user of the medicinal product is anticipated, for example for inhalation or dermal contact, these routes should be studied.

The LD50 studies need not be performed if sufficient data is generated by other methods to satisfy the requirements of the medicines authority.

1.4 Approximate LD

In order to reduce the number and suffering of the animals involved, new protocols for single dose toxicity testing are continually being developed. Studies carried out in accordance with these new procedures when properly validated will be accepted, as well as studies carried out in accordance with established internationally recognized guidelines. The "fixed dose procedure" proposed by the British Toxicological Society could be followed (e.g. Van den Heuvel *et al.* 1990. *Fd. Chem. Toxic.* Vol 28, 469-482).

All studies must be done on the active ingredient. If acute toxicity studies with the formulation are available these should also be submitted.

1.5 Subacute toxicity

Repeat-dose toxicity tests are intended to reveal any physiological and/or pathological changes induced by repeated administration of the active substance or combination of active substances under examination, and to determine how these changes are related to dosage.

In the case of substances or medicinal products intended solely for use in animals that do not produce food for human consumption, a repeat-dose toxicity study in one species of experimental animal will normally be sufficient. This study may be replaced by a study conducted in the target species. The frequency and route of administration, and the duration of the study should be chosen having regard to the proposed conditions of clinical use. The investigator shall give reasons for the extent and duration of the trials and the dosages chosen.

In the case of substances or medicinal products intended for use in food producing animals, the studies should be conducted in at least two species, one of which should be a non-rodent. The investigator shall give reasons for the choice of species, having regard to the available knowledge of the metabolism of the product in animals and man. The test substance shall be administered orally. The duration of some of the studies shall be at least 90 days. The investigator shall clearly state and give reasons for the method and frequency of administration and the length of the trials.

The maximum dose should normally be selected so as to bring harmful effects to light. The lowest dose level should not produce any evidence of toxicity.

Evaluation of the toxic effects shall be based on observation of behaviour, growth, haematology and physiological tests, especially those relating to the excretory organs, and also autopsy reports and accompanying histological data. The choice and range of each group of tests depends on the species of animal used and the state of scientific knowledge at the time.

In the case of new combinations of known substances which have been investigated in accordance with the provisions of this Directive, the repeated-dose tests may,

except where toxicity test have demonstrated potentiation or novel toxic effects, be suitably modified by the investigator, who shall submit his reasons for such modifications.

1.6 Chronic toxicity and carcinogenicity studies

Where applicable long-term toxicity determinations i.e. one year chronic study in dogs or a lifetime chronic study in rats, may be required.

Long-term animal carcinogenicity studies will usually be required for substances to:

- which human beings will be exposed,
- which have a close chemical analogy with known carcinogens,
- which during mutagenicity testing produced results indicate a possibility of carcinogenic effects
- which gave rise to suspect signs during toxicity testing.

1.7 Mutagenicity/Clastogenicity

Mutagenicity tests are intended to assess the potential of substances to cause transmissible changes in the genetic material of cells. If there is any indication of mutagenicity, carcinogenicity studies will be required.

Any new substances intended for use in veterinary medicinal products must be assessed for mutagenic properties.

The number and types of tests and the criteria for the evaluation of the results shall depend on the state of scientific knowledge when the application is submitted.

1.8 Reproductive toxicity

Reproductive studies will be required if there is any indication of adverse effects on potential reproduction in the preceding preclinical studies.

The purpose of such studies is to identify possible impairment of male or female reproductive function or harmful effects on progeny resulting from the administration of the medicinal products or substance under investigation.

In the case of substances or medicinal products intended for use in food-producing animals, the study of the effects on reproduction shall be carried out in the form of a two-generation study on at least one species, usually a rodent. The substances or product under investigation shall be administered to males and females from an appropriate time prior to mating. Administration should continue until the weaning of the F2 generation. At least three dose levels shall be used. The maximum dose should be selected so as to bring harmful effects to light. The lowest dose level should not produce any evidence of toxicity.

Evaluation of the effects on reproduction shall be based upon fertility, pregnancy and maternal behaviour; suckling growth and development of the F1 offspring from conception to maturity and the development of the F2 offspring to weaning.

1.9 Study of embryotoxic/foetotoxic effects including teratogenicity

Embryotoxic/foetotoxic, including teratogenicity studies will be required :

- In the case of substances or medicinal products intended for use in food-producing animals, studies of embryotoxic/foetotoxic effects, including teratogenicity, shall be carried out. These studies shall be carried out in at least two mammalian species, usually a rodent and the rabbit. The details of the test (number of animals, doses, time at which administered and criteria for the evaluation of results) shall depend on the state of scientific knowledge at the time the application is lodged and the level of statistical significance that the results should attain. The rodent study may be combined with the study of effects on reproductive function.

- In the case of substances or medicinal products which are not intended for use in food-producing animals, to animals which might be used for breeding, a study of embryotoxic/foetotoxic effects, including teratogenicity, shall be required in at least one species, which may be the target species.

1.10 Neurotoxicity

Neurotoxicity studies will be required if there is any indication of such effects in the preceding preclinical studies or if the product is chemically related to a group with such potential.

1.11 Other requirements

1.11.1 Immunotoxicity

- Where the effects observed during repeated dose studies in animals reveal specific changes in lymphoid organ weights and/or histology and/or changes in the cellularity of lymphoid tissues, bone marrow or peripheral leukocytes, the investigator shall consider the need for additional studies of the effects of the product on the immune system.

The state of scientific knowledge at the time the application to be is submitted shall be taken into account when designing such studies and evaluating their results.

1.11.2 Microbiological properties of residues

1.11.2a Potential effects on the human gut flora

The microbiological risk presented by residues of anti-microbial compounds for the human intestinal flora shall be investigated in accordance with the state of scientific knowledge at the time the application is submitted.

1.11.2b Potential effects on the microorganisms used for industrial food processing

In certain cases, it may be necessary to carry out tests to determine whether residues cause difficulties affecting technological processes in industrial foodstuff processing *e.g.* cheese production..

1.11.3 Observations in humans

Information shall be provided showing whether the constituents of the veterinary medicinal product are used as medicinal products in human therapy. If this is so, a report should be compiled on all the effects observed (including side-effects) in humans. This may be important for assessment of the veterinary medicinal product. When constituents of the veterinary medicinal products are no longer used as medicinal products in human therapy, the reasons should be stated.

Where a medicinal product is intended for topical use, systemic absorption shall be investigated in the target species of animal. If it is proved that systemic absorption is negligible, the repeated dose toxicity tests, the tests for reproductive toxicity and the carcinogenicity tests may be omitted, unless:

- under the conditions of use laid down, oral ingestion of the medicinal products by the animal is to be expected, or
- the medicinal particular may enter foodstuffs obtained from the treated animal (intra-mammary preparations).

2 SAFETY STUDIES IN TARGET SPECIES

2.1 Tolerance studies

In accordance with the guidelines (Evaluation of the safety of veterinary medicinal products for the target animals) provided in terms of Directive 81/851/EEC as amended should be followed. Details should be provided of any signs of intolerance which have been observed during studies conducted in the target species. The studies concerned, the dosages at which the intolerance occurred and the species and breeds concerned should be specified. Details of any unexpected physiological changes should also be provided.

To assess the safety of the compound being applied for the formulation should be tested at multiples of the recommended dose/concentration until signs of intoxication is induced in at least one animal of each sex. A ten fold overdose need not be exceeded. If applicable, the degree of irritation that the formulation causes following administration should also simultaneously be assessed.

2.2 Reproductive safety studies

Reproductive safety studies in the target species will be required if there is any indication of adverse effects on potential reproduction in the preceding trials.

2.3 Field safety studies

In food-producing animals the safety of the formulation should be extensively tested under a wide variety of local field conditions at least double the recommended dose/concentration.

3 ENVIRONMENTAL SAFETY STUDIES

.3.1 Ecotoxicity

The purpose of the study of the ecotoxicity of a veterinary medicinal product is to assess the potential harmful effects which the use of the product may cause to the environment and to identify any precautionary measures which may be necessary to reduce such risks.

An assessment of ecotoxicity shall be compulsory for any application for marketing authorization for a veterinary medicinal product other than applications submitted in accordance with point 10 of Article 5, second paragraph, of Directive 81/851/EEC.

This assessment shall normally be conducted in two phases.

PRECLINICAL SAFETY STUDIES

- In the first phase, the investigator shall assess the potential extent of exposure to the environment of the product, its active ingredients or relevant metabolites, taking into account:
- the target species, and the proposed pattern of use (for example, mass-medication or individual animal medication),
- the method of administration, in particular the likely extent to which the product will enter directly into environmental systems.
- the possible excretion of the product, its active ingredients or relevant metabolites into the environment by treated animals and in particular persistence in such excreta,
- the disposal of unused or waste product.

- In a second phase, having regard to the extent of exposure of the product to the environment and the available information about the physical/chemical, pharmacological and/or toxicological properties of the compound which has been obtained during the conduct of the other tests and trials required by this Directive, the investigator shall consider whether further specific investigation of the effects of the product on particular eco-systems is necessary.

If appropriate, further investigation may be required of:

- fate and behaviour in soil,
- fate and behaviour in water and air and
- effects on aquatic organisms,

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GUIDELINE ON EFFICACY OF VETERINARY BIOLOGICAL MEDICINES

This guideline has been prepared to serve as a recommendation to applicants wishing to submit data as evidence of efficacy for veterinary biological medicines. It represents the Medicines Control Council's current thinking on this topic. It is not intended as an exclusive approach and does not bind the MCC nor confirm any rights for or on any person. Alternative approaches may be used but must be scientifically justified. The MCC is committed to ensure that all medicines gaining market approval will be of the required quality, safety and efficacy.

REGISTRAR OF MEDICINES
MS M. P. MATSOSO
DATE: 30-05-2003

EFFICACY OF VETERINARY BIOLOGICALS

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PURPOSE

(1) Guidelines are to be re-evaluated from time to time and amended if necessary.

(2) Deviations from these guidelines may be acceptable, provided that they are scientifically justified.

(3) The Regulatory Authority will, in the case of a biological destined for use in production animals, evaluate the proposed administration of the product to ensure that it is in line with local husbandry practices.
An evaluation of efficacy will also be done in light of the specific strains of local organism(s) that are present.

(4) Purpose:

The purpose of efficacy data to be submitted for the registration of veterinary biologicals is to prove that the use of the product according to the label claims (as far as recommended age, route of administration and type of species are concerned), should have the desired effect as claimed on the label.

I. GENERAL DATA:

The efficacy of the product is firstly dependent on the quality of the product. This is determined by the nature and quality of the starting materials and the manufacturing process. Quality control procedures employed during the production process and quality control tests that are carried out on the starting materials and the final product will ensure the quality of the biological. The efficacy of the administration of the product is subsequently proved in the target species, according to the directions for use on the label/package insert.

The following information is required:

(1) Basic information on the product:

(a) Strain(s) present in the product

(b) History of strain

(c) Manipulation of strain (number of passages)

(d) Composition of final product:

(i) Each component:
- description
- function
- reference

(ii) Percentage moisture in the case of live vaccines

(iii) Percentage inactivant in the case of inactivated vaccines

(2) Manufacture:
- (a) Outline of Production:
- (b) Starting materials (Reference or proof of quality):
  - (i) Starting materials listed in a pharmacopoeia
  - (ii) Materials of biological origin:
    - (i) Specific pathogen free eggs
      -Flock tests (type of test, sampling frequency)
    - (ii) Other
      - primary cells
      - cell lines
      - Specific products of animal origin (body fluids, secretions)
  - (iii) Starting materials of non-biological origin, not listed in a pharmacopoeia
  - (iv) In-house preparation of media

(3) Quality assurance during production:
- (a) Quality control procedures:
  - Flow chart of production and quality control procedures
  - Description of tests:
  - Results of 3 consecutive production runs

(4) Control tests on finished product:
- (a) Description of tests, including potency tests
- (b) Results of tests on 3 consecutive production batches

(5) Stability/shelf life:
- (a) Storage conditions
- (b) Proposed shelf life
- (c) Justification of proposed shelf life of:
  - (i) Finished product:
    - data required for at least three batches
    - data included for at least three months after the proposed expiry date
  - (ii) Reconstituted product (if applicable)

II SPECIFIC EFFICACY DATA:

The following data is required:

(1) Biological properties of the organism(s) used in the vaccine.

(2) Proof of the efficacy of the product with the exact composition as stated in I(1)(d). This would include the specific strain of organism, at the highest passage level from the master seed that is permitted in the Outline of Production, with the exact same type and volume of excipients in the final product. These would be inclusive of (but not exclusively) any stabilizer, traces of cell culture medium etc*

(3) Proof of the efficacy of the exact product to be registered for the minimum recommended age of administration.*

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(4) Proof of the efficacy of the exact product to be registered for each species indicated on the label. *

(5) Proof of the efficacy of the exact product to be registered for each route of administration as mentioned on the label in each of the species mentioned.
Note: Different intramuscular injection sites require separate efficacy data*

(6) * Efficacy data should *in all cases* include data for the *minimum guaranteed titer (antigen level).*

(7) Efficacy data should consist of relevant laboratory as well as field studies:
(a) Laboratory studies:

(i) Determination of the minimum protective dose

(ii) Determination of the duration of immunity (DOI)

(iii) Statistically valid vaccination-challenge studies in each of the host animal(s) for which the product is recommended, at the youngest recommended age, for each recommended route of administration.
Studies should be carried out under controlled conditions, starting whenever possible, with sero-negative animals.
Challenge should be carried out with an acceptable strain of organism with a suitable level of pathogenicity.

Alternatively:
Suitably validated potency tests could be carried out in laboratory animals

(b) Field studies:
Field studies should be carried out with the exact formulation to be registered, in the species, age and route(s) of administration as recommended
Artificial challenge with a pathogenic strain is not required.

(8) All trial data should consist of:
(i) Properly documented scientific trial data

(ii) An indication should be supplied of the person responsible for the trial (designation), the trial site as well as the trial date.

(iv) Exact trial procedure:
a. Numbers used
b. Exact dosages/titers
c. Details of route of administration

(v) Results:
a. Should be supplied in detail
b. Abbreviations in tables, graphs should be explained
c. A statistical analysis of the results should be included

(8) Efficacy data for a multi-component biological may be used to prove the efficacy of a biological that only contains one or more of the components, provided that the composition of the biologicals (apart from the active ingredient(s)) are identical.

(9) Autogenous biologicals:

(a) Data to be submitted on the efficacy of autogenous vaccines may consist of:
(i) laboratory trial data obtained by the applicant
(ii) information obtained from the literature

If it is impractical to obtain laboratory data prior to the application and if information is not available from the literature, the applicant should submit a suitable motivation for exemption from the submission of efficacy data as mentioned in point 9 (a)(i), and (ii).

Efficacy data will be obtained through the application of the biological and needs to be submitted at the end of 12 months. No challenge work is required, but the veterinarian under whose supervision the biological is used, has to monitor the situation and keep records.

III. ADDITIONAL EFFICACY DATA

1. Interference tests:
(a) If the product contains two or more antigenic components, the absence of interference between the two components (decrease in the protective immunological response to one of the components) should be proved.

(b) If an inactivated liquid product is used as a diluent for a desiccated live vaccine, proof must be submitted that there is no bactericidal or virucidal activity due to residual inactivating agent in the inactivated liquid product.

(c) The absence of possible interference between two different vaccines from the same manufacturer that are recommended to be given to the same animal within a 2-week period also has to be proved.

IV. REFERENCES:

1. United States Department of Agriculture (USDA) (1999). Code of Federal Regulations, Title 9, Parts 1-199. US Government Printing Office, Washington D.C., USA.

2. Office International des Epizooties (OIE) (2000) Manual of Standards for Diagnostic Tests and Vaccines.

3. European Agency for the Evaluation of Medicinal Products (EMEA) (2002) 7 Westferry Circus, Canary Wharf, London, E14 4HB, UK.

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SAFETY OF VETERINARY BIOLOGICAL MEDICINES

This guideline has been prepared to serve as a recommendation to applicants wishing to submit data as evidence of safety for veterinary biological medicines. It represents the Medicines Control Council's current thinking on this topic. Alternative approaches may be used but must be scientifically justified. The MCC is committed to ensure that all medicines gaining market approval will be of the required quality, safety and efficacy.

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GUIDELINES

General:

(1) Guidelines are to be re-evaluated from time to time and amended if necessary.

(2) Deviations from these guidelines may be acceptable, provided that they are scientifically justified.

(3) The feasibility of the registration of a biological will be evaluated by the Regulatory Authority to ensure that the use of the product will not introduce an unwanted foreign organism into the country (live vaccine) or cause sero-conversion in animals that will have a negative impact on serological surveys or animal disease control programmes (inactivated vaccines).

(4) Purpose of submission of safety data:

The purpose of safety data to be submitted for the registration of veterinary biologicals is to prove that the use of the product according to the labels claims (as far as recommended age, route of administration and type of species are concerned), does not pose any danger to the life, general well-being or production potential of the animal to be vaccinated.
The evaluation of the safety of the use of the product is also of prime importance to human health to ensure that no harmful residues are present in animals that are destined for human consumption.

I GENERAL DATA:

The safety of the product is firstly dependent on the quality of the product. This is determined by the nature and quality of the starting materials and the manufacturing process. Quality control procedures employedduring the production process and quality control tests that are carried out on the starting materials and the final product will determine the absence of extraneous agents (viruses, bacteria, fungi etc) that could influence the safety of the product. The safety of the administration of the product is subsequently proved in the target species, according to the directions for use on the label/package insert.

The following information is required:

1) Basic information on the product:
   (a) Strain(s) present in the product

   (b) History of strain

   (c) Manipulation of strain (number of passages)

(d) Composition of final product:

(i) Each component:
- description
- function
- reference

(ii) Percentage moisture in the case of live vaccines
(iii) Percentage inactivant in the case of inactivated vaccines

(2) Manufacture:
(a) Outline of Production:

(b) Starting materials (reference or proof of quality):
(i) Starting materials listed in a pharmacopoeia
(ii) Materials of biological origin:
(i) Specific pathogen free eggs
-Flock tests (type of test, sampling frequency)

(ii) Other
- primary cells
- cell lines
- Specific products of animal origin (body fluids. secretions)
- Evaluation of risk of transmission of TSE (transmissible Spongiform Encephalopathy agents)

(iii) Starting materials of non-biological origin, not listed in a pharmacopoeia

(iv) In-house preparation of media

(3) Quality assurance during production:
(a) Quality control procedures:
- Flow chart of production and quality control procedures
- Description of tests:
- Results of 3 consecutive production runs

(4) Control tests on finished product:
(a) Description of tests
(b) Results of tests on 3 consecutive batches

(5) Stability/shelf life:
(a) Storage conditions
(b) Proposed shelf life
(c) Justification of proposed shelf life of:
(i) Finished product:
- data required for at least three batches
- data included for at least three months after the proposed expiry date
(ii) Reconstituted product (if applicable)

II SPECIFIC SAFETY DATA:

The following data are required:

(1) Biological properties of the organism(s) used in the vaccine.

(2) Proof of the safety of the product with the exact composition as stated in I(1)(d). This would include the specific strain of virus or bacterium, at the passage level as stated, with the exact same type and volume of excipients in the final product. These would be inclusive of (but not exclusively) any stabilizer, traces of cell culture medium etc

(3) Proof of the safety of the exact product to be registered for the minimum recommended age of administration. *

(4) Proof of the safety of the exact product to be registered for each species on the label. *

(5) Proof of the safety of the exact product to be registered for each route of administration as mentioned on the label in each of the species mentioned.
Note: Different intramuscular injection sites require separate safety data*

(6) Safety data should include the following:*
- (a) Safety data for the administration of a single dose
- (b) Safety data for the administration of an overdose (x10 for live and x2 for inactivated products)
- (c) Revaccination:
  If revaccination is recommended on the label, proof of the safety of a repeated administration has to be submitted.
  Note: This requirement is not applicable if a single administration is recommended only.

* Note: If a test in a laboratory animal (e.g. guinea pig or mouse) is used, proof of validation of the test for this purpose has to be supplied.

Mouse safety tests are applicable to bacterins, toxoids, bacterin-toxoids and bacterial extracts, unless the product is inherently lethal to mice, in which case a guinea pig safety test is used. If the product is recommended for use in poultry, safety tests are carried out in poultry. Products that are recommended for use in fish, other aquatic species or reptiles are tested for safety in the target species.

Inactivated virus vaccines are either safety tested in the host animal, or a mouse or guinea pig safety test is used. Inactivated vaccines for use in poultry are always safety tested in poultry.

(7) Field safety tests:
All veterinary biological products destined for use in production animals should be tested for safety in the field. Field safety studies are destined to detect unexpected reactions, including mortality that may not have been observed during the development of the product. The tests should be done in the target species, preferably at a variety of geographical locations, using a sufficient number of susceptible animals. The test animals should represent all the ages and husbandry practices for which the product is indicated. A protocol should be developed indicating the observation and recording methods.
Field safety tests could be combined with field efficacy tests.

(8) Safety data for a multi-component biological may be used to prove the safety of a biological that only contains one or more of the components, provided that the composition of the biologicals apart from the active ingredient(s) are identical.

(9) All trial data should consist of:

(a) Properly documented scientific trial data.
An indication should be supplied of the person responsible for the trial (designation), the trial site as well as the trial date.

(b) Exact trial procedure:
(i) Numbers used
(ii) Exact dosages/titres
(iii) Details of route of administration

(c) Results:
(i) Should be supplied in detail
(ii) Abbreviations in tables, graphs should be explained
(iii) A statistical analysis of the results should be included

(10) Autogenous biologicals:

(a) Autogenous vaccines may only consist of micro-organisms either proven to be safe or rendered safe by inactivation.

(b) The safety of an autogenous vaccine should be satisfactorily proven prior to authorisation for use in the case of poultry vaccines or where possible. In the case of a vaccine for use in large animals if testing in the applicable species is not practical prior to authorisation, the lack of safety testing should be indicated on the label and the user advised. The user should also be advised that the vaccine is to be initially administered to five animals on the farm and these animals monitored for adverse reactions.

III ADDITIONAL SAFETY DATA:

(1) Examination of reproductive functions particularly in the case of modified live biologicals:
Safety data are not required if the product is not indicated for use in animals of a reproductive age

(2) Examination of immunological functions:
Safety data are not required if:
(i) The product is an inactivated vaccine
(ii) The active ingredient is not immunosuppressive
(iii) The active ingredient in its natural form does not affect organs of the immune system

(3) Spread of the vaccine strain:
Data have to be submitted to prove the safety of the product as far as the excretion by and the spread of the vaccine strain by the most sensitive category of the target species.

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(4) Data have to be submitted to prove the safety of the unintended spread of the vaccine strain to susceptible animals of a non-target species that is also susceptible to infection by the organism(s) in the vaccine

(5) Dissemination in the vaccinated animal:

Data have to be submitted for the most sensitive category of the target species

(6) Reversion to virulence:

In the case of a virus vaccine:
Data have to be submitted to compare the virulence of the vaccine virus after 10 *in vivo* back passages (in the case of poultry vaccines) or 5 *in vivo* back passages (in the case of vaccines other than for use in poultry) of the vaccine virus with the parental wild type virus in the most sensitive category of the target species.

(7) Recombination or genomic re-assortment:

An evaluation of the possibility of recombination or genomic re-assortment should be submitted.

(8) Residues:

Data on the presence and safety of residues in the target species should be submitted.
In the case of an inactivated vaccine (adjuvants) or a live vaccine (preservatives), residues could either pose a human health hazard or lead to aesthetically unacceptable lesions at the injection site that could lead to condemnation at the abattoir in the case of animals destined for human consumption.

(9) Interactions:

Data are required to prove the safety of the biological product if used in combination with other products.

(10) Ecotoxicity:

An assessment of the risk to the environment of the use of the product has to be submitted.

The risk assessment should include:

1. Hazard identification
   (a) Capacity of the live organism to transmit to non-target species
   (b) Shedding of live product organisms (route, numbers, duration)
   (c) Capacity to survive, establish and disseminate
   (d) Pathogenicity to other organisms
   (e) Potential for other effects of the live product organism

(f) Toxic effects of the product components

(g) Toxic effects of excreted metabolites

2. Assessment of likelihood of a hazard occurring

3. Assessment of the consequences of a hazard occurring

4. Assessment of level of risk.

(11) Safety of biotechnology-derived vaccines:
Biotechnology-derived products do not differ fundamentally from conventional products and the existing guidelines would apply to these products as well.
It should be ensured that the use of these products does not pose a threat to either public health or the environment.

These products can be divided into three categories, based on their biological properties and on the safety concerns that they represent:

Category I:
Non-viable or killed products that pose no risk to the environment and present no new or unusual safety concerns. Such products include inactivated micro-organisms, either whole or as sub-units, created by using rDNA.

Category II:
Products that contain live micro-organisms modified by adding or deleting one or more genes. Added genes may code for marker antigens, enzymes or other biochemical by-products. Deleted genes may code for virulence, oncogenicity, marker antigens, enzymes or other biochemical by-products.
The application must include a characterisation of the DNA segments added or deleted, as well as a phenotypic characterisation of the altered organism. The genetic modification must not result in any increase in virulence, pathogenicity or survivability in the altered organism in comparison with the wild-type form. It is important that the genetic modification does not cause deterioration in the safety characteristics of the organism.

Category III:
These products make use of live vectors to carry recombinant-derived foreign genes that code for immunising antigens. Live vectors may carry one or more foreign genes that have been shown to be effective for immunising target host animals.

IV. REFERENCES:

1. United States Department of Agriculture (USDA) (1999). Code of Federal Regulations, Title 9, Parts 1-199. US Government Printing Office, Washington D.C., USA.

2. Office International des Epizooties (OIE) (2000) Manual of Standards for Diagnostic Tests and Vaccines.

3. European Agency for the Evaluation of Medicinal Products (EMEA) (2002) 7 Westferry Circus, Canary Wharf, London, E14 4HB, UK.

VMRF 1

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

APPLICATION FOR REGISTRATION OF A VETERINARY MEDICINE

ADMINISTRATIVE DATA

APPLICATION NUMBER

A. PARTICULARS OF PROSPECTIVE HOLDER OF THE CERTIFICATE OF REGISTRATION

Name: ----------
Business address: ----------
Postal address: ----------
Telephone No: ----------
Fax No: ----------
E-Mail address: ----------
Site Master File Number: ----------

Authorised person/applicant to communicate with regulatory authority on behalf of the holder of the certificate of registration

Name: ----------
Business address: ----------

Telephone no: ----------
Fax No.: ----------
E-mail: ----------

(Attach letter of authorisation signed by the Managing Director)

VMRF 1

B. PARTICULARS OF VETERINARY MEDICINE

Proprietary name: ----------

Pharmacological Classification: ----------

Dosage form:----------

Dosage unit:----------

Active pharmaceutical ingredient(s) and strength(s) per dosage unit:

Descriptive name of veterinary biological:----------

Indicate with an X in the appropriate block if the application is for a

☐ New product with new active ☐ new product with existing active

Amendment to existing product. Registration no. ☐☐☐☐☐☐☐

Parallel product ☐ daughter product ☐ multi – source product

Route of administration: ----------

Pharmacological classification:----------

Manufacturer:----------

Business address:----------

Site Master File reference number: ----------

Packer: ----------

Business address:----------

Site Master File reference number: ----------

Final product release control (FPRC):----------

Business address:----------

Site Master File reference number: ----------

Final product release responsibility (FPRR):----------

Business address: ----------

Site Master File number: ----------

The undersigned hereby declares that all the information herein and in the PARTS hereto are correct and true and are relevant to this particular medicine.

.....

Signature of Managing Director/Authorised person

....

Name in block letters Date of application

....

Designation Date of current amendment **(Post-registration only)**

VMRF 1

C. UPDATE HISTORY (**For Post-registration only**)

LETTER DATE OF APPLICATION FOR AMENDMENT	SUMMARISED DETAILS OF AMENDMENT	DATE OF APPROVAL BY COUNCIL

Guideline references:

VMRF 1

TECHNICAL DATA

PART 1 A

PARTICULARS OF THE VETERINARY MEDICINE SCIENTIFIC PACKAGE INSERT

The under-mentioned information with regard to this medicine shall appear on the scientific package insert. The information shall be presented in the format stipulated: Provided that the Council may authorise any deviation from such information or such format (refer to Regulation 40).

1. The words "**Veterinary Medicine**"
2. Scheduling status
3. Proprietary name and dosage form
4. Scheduling status
5. Dosage form
6. Composition
7. Pharmacological classification
8. Pharmacological action
   Pharmacokinetics and pharmacodynamics
9. Indications per species.
10. Contra-indications
11. Warnings or withdrawal period in the case of food-producing animals
    Safety in pregnancy and lactation
12. Dosage and directions for use including age and species dosage
13. Side effects and special precautions for use per species. Interactions
14. Known signs of overdosage and particulars of its treatment per species
15. Conditions of registration
16. Identification
17. Presentation
18. Storage instructions
19. Registration number
20. Name and business address of the holder of the certificate of registration
21. Date of publication of the package insert

VMRF 1

PART 1 B SPECIMEN OF THE LABEL

A specimen of the immediate container label and, if applicable, the outer label shall be included here. This shall conform to Regulation 48.

VMRF 1

PART 1 C FOREIGN REGISTRATION

a) A list of countries in which an application has been lodged and the status of these applications shall be furnished, detailing approvals, deferrals, withdrawals and rejections.

b) If the veterinary medicine has been registered in another country, the conditions of registration and proof thereof shall be furnished. If registered in the European Union commission (including countries employing the mutual recognition system), Australia, United Kingdom, United States of America, Canada, The Netherlands, Sweden and Japan, the approved package insert (data sheet) shall be provided (All documents must be submitted in English).

c) Name and business address of the manufacturer, packer and testing laboratory, where applicable.

d) Details of any negative decision by any recognised Medicines Regulatory Authority shall be Provided.

VMRF 1

PART 2

QUALITY CONTROL

PART 2A (i) VETERINARY MEDICINES OTHER THAN BIOLOGICALS

ACTIVE PHARMACEUTICAL INGREDIENT REQUIREMENT (DEVELOPMENT CHEMISTRY AND CHARACTERISATION)

a) The name(s), structural formulae, empirical formulae, molecular mass, solubility and storage requirements are as follows:

International Nonproprietary Name (INN) or approved name and chemical name	Structural formula, empirical formula, molecular mass	Solubility	Storage requirements	Shelf-life (and re-test period)

b) The active pharmaceutical ingredients are obtained from the following sources:
Name and business address of the manufacturer(s)

c) Active Pharmaceutical Ingredient File (APIF) or DMF (open part) or certificate of suitability (CEP)

d) Certificate of analysis of two batches

e) Proof of physical and chemical equivalence (more than one manufacturer)

f) Stability data and shelf-life of active pharmaceutical ingredient

VMRF 1

PART 2A (ii) PRIMARY PRODUCTION LOT/BATCH (BIOLOGICAL VETERINARY MEDICINES)

1. DESCRIPTION OF THE PREPARATION AND PRODUCTION OF THE PRIMARY PRODUCTION LOT.

a) Name and address of the manufacturing facility in which production of the primary production lot takes place.

b) Master seed Identification , description and control

c) The complete description of the preparation and manufacturing process of the primary production or bulk lot, the tests carried out on the product and the stages at which such tests are carried out to confirm the integrity of the product must be submitted.

2. SPECIFICATIONS OF RAW MATERIALS USED IN THE PRIMARY PRODUCTION LOT.

The following are the specifications that apply to the raw materials used in the primary production or bulk lot of a veterinary biological medicine, including the titles of the tests and the limits and criteria of acceptance of each parameter contained in the specification. (Where the test mentioned corresponds to a recognised pharmacopoeia, the source shall be mentioned):

3. TESTS CARRIED OUT ON RAW MATERIALS IN THE PRIMARY PRODUCTION LOT AND THE LABORATORIES

The following is a complete description of the tests carried out on all the raw materials used in the primary production or bulk lot, specifying the name and address of the laboratory(ies) in which such tests are carried out.

VMRF 1

PART 2 B (i) FORMULATION

FORMULATION OF THE FINAL DOSAGE FORM

a) Below is a schedule of the names and quantities of each active and inactive ingredient contained in a dosage unit. Where no dosage unit exists, other suitable unit of mass or volume of the veterinary medicine may be used and these shall conform to the relevant particulars in the package insert and on the label with regard to the active pharmaceutical ingredients.

b) The purpose(s) of each inactive ingredient in the formulation shall be specified, including that of raw materials used in manufacturing, but which are not present in the final product.

Approved name	Quantity per dosage unit*	Active or inactive	Purpose of inactive

*mg per tab/cap/loz/supp or mg or ml per specified volume or mass of product

c) Potency calculations. A statement to the effect that the actual quantity of the active pharmaceutical ingredient will depend on the potency shall be included.

d) Composition of inactive ingredients in combination, mixtures, etc.

e) Overages and justification for their inclusion.

f) Toxicity level per dosage unit must be indicated for all solvents and for other ingredients when required by Council. Levels must be indicated as per "USP DI" or "Martindale", or "The Complete Drug Reference", or other specified reference.

VMRF 1

PART 2 B (ii) FORMULATION OF THE FINAL FILLING LOT FOR VETERINARY BIOLOGICALS

a) Below is a schedule of the names and the strength or concentration of each active and inactive in the veterinary biological veterinary medicine and with regard to the active ingredients , conform to the relevant particulars in the package insert and on the label .

b) The purpose of each ingredient in the formulation shall be specified, and raw materials used. even if not present in the final dosage form but used during manufacture , shall be mentioned.

Approved name or chemical name of constituent	Quantity per unit *	Purpose	Purpose of inactive

*%m/m,m/v,v/v

VMRF 1

SECTION3B(iii) FORMULATION OF THE RECONSTITUTING LIQUID FOR THE FINAL FILLING LOT FOR BIOLOGICAL VETERINARYMEDICINES

(a) Below is a schedule of the names and quantities of each ingredient contained in the diluent.

(b) The purpose of each ingredient in the formulation shall be specified , and raw materials used , even if not present in the final diluent shall also be given .

Approved name or chemical name of constituent	Quantity	Purpose

VMRF 1

PART 2C SPECIFICATIONS AND CONTROL PROCEDURES FOR RAW MATERIALS USED IN THE MANUFACTURE OF THE FINAL PRODUCT (VETERINARY MEDICINES) OR FINAL FILLING LOT AND DILUENTS (BIOLOGICALS)

a) Pharmacopoeial ingredients.

Raw Material		Specifications and Pharmacopoeial reference*	Limits	Additional Tests (e.g. particle size)
Active				
Inactive				

*The latest edition of the pharmacopoeia is implied, unless otherwise specified and justified.

(b) Non-pharmacopoeial ingredients. In – house specifications and control procedures for these ingredients should be included .

Raw Material		Specifications	Limits	In-house control procedures
Active				
Inactive				

c) The applicant must comply with and confirm the following requirements in the application:

(i) Identification and assay of the active raw material, irrespective of the possession of a certificate of analysis from the supplier.

(ii) Identification of the inactive raw material, irrespective of the possession of a certificate of analysis from the supplier.

(iii) Perform any other tests not included in a valid certificate of analysis.

d) The frequency of testing of water, where applicable, must be included

VMRF 1

PART 2 D CONTAINER AND PACKAGING MATERIAL

a) DESCRIPTION OF CONTAINERS

(i) Immediate container, including any patient-ready packs, closure, wadding, desiccant (type of material and dimensions, including sketches).

(ii) Outer container (type of material of container).

(iii) Bulk container (type of material of container).

(iv) Application and administrative sets (type of material and dimensions including sketches).

b) SPECIFICATIONS AND LIMITS FOR PACKAGING MATERIALS

The following must be completed :

Specification	Limit	Name of manufacturer/packer of the final product

Indicate those tests performed by the supplier of the packaging material.

c) **DESCRIPTION OF CONTROL PROCEDURES PERFORMED BY MANUFACTURER/PACKER OF FINAL PRODUCT**

d) PACK SIZES

VMRF 1

PART 2 E MANUFACTURING PROCEDURES

MANUFACTURING PROCEDURES OF FINAL PRODUCT (VETERINARY MEDICINES)

FINAL FILLING LOT AND DILUENT (BIOLOGICAL VETERINARY MEDICINES)

a) INSPECTION FLOW DIAGRAM:

b) MANUFACTURING PROCEDURES:

(i) Batch Manufacturing Formula(s) and Batch Size(s)

(ii) Copy of the Batch/Master Manufacturing document for a real batch. A comprehensive flow diagram or a description of the manufacturing procedures detailing the various stages of manufacturing. Indicate the type of equipment, sieve sizes (µm), duration of treatment, temperature, light and humidity conditions, machine settings (e.g. rotation speed or rpm), etc. The frequency of all in-process control tests (analytical, microbiological, and physical) shall be shown in the flow diagram or specified in the description.

c) PACKAGING PROCEDURES:

Copy of the Batch/Master Packaging document or a comprehensive flow diagram or a description of the packaging procedures detailing the various stages of packaging and labeling. Indicate the type of equipment used in the packaging process. The in-process tests, the frequency of testing and control procedures carried out during the packaging process shall be included.

d) MANUFACTURING PROCESS VALIDATION PROTOCOL:

The process validation protocol is as follows:

VMRF 1

PART 2 F FINISHED PRODUCT (VETERINARY PHARMACEUTICAL)

FINAL FILLING LOT & DILUENT (VETERINARY BIOLOGICAL)

a) SPECIFICATIONS AND LIMITS

The following tables include the specifications , limits criteria for acceptance of all physical , chemical and , where applicable , microbiological parameters and the responsible laboratories for :

(i) in - process control

Specification	Limits	Responsible Laboratory (ies)

(ii) Final product control

Specification	Limits	Responsible Laboratory (ies)

(iii) Stability studies

Specification	Limits	Responsible Laboratory (ies)

(iv) Manipulated final product

Specification	Limits	Responsible Laboratory (ies)

Final product specifications , for imported products upon local receipt the product must be re – identified and assayed , unless a supplier / transport validation has been submitted to and approved by Council. In all cases a valid Certificate of Analysis which shows all the tests described in the final product specification must accompany the shipment . Should any of the required tests be omitted from the CoA , then these tests must be re – done locally prior to the release.

b) TABLE OF TESTS TO BE PERFORMED

	TITLE OF SPECIFICATION
FPRC	
FPRC responsible for tests after importation	Identification Assay

VMRF 1

FPRR	Appearance of dosage form Container Package insert Label Batch No. Expiry date. Certificate of Analysis Batch release documents

c) **CONTROL PROCEDURES**

Description of the control procedures for all the specifications in section (a) must be included

d) **CERTIFICATE OF ANALYSIS OF THE FINAL PRODUCT**

e) **VALIDATION**

Validation data for all quantitative assay methods must be included.

It must be demonstrated that the assay method is stability indicating , i.e. will distinguish between the active ingredient and the degradation product (s). If the assay method is not stability indicating the validation data of the procedures used to determine the assay and that used to determine the degradation product must be submitted separately.

VMRF 1

PART 2 G STABILITY DATA FOR THE FINISHED PRODUCT

a) **STABILITY PROGRAMME**

Describe the stability programme to be followed and include, the following:

(i) Conditions (temperature, humidity)

(ii) Time points of determination, e.g. 0, 3, 6, 9 months, etc.

(ii) Specifications to be determined

(iii) Frequency of stability testing on future batches (Refer to WHO and cGMP stability testing guidelines.)

(iv) Stability test control procedures

b) **PRESENTATION OF STABILITY DATA**

Product Name: Batch No.: Batch Size: Date of Manufacture:				Packaging (material and pack sizes): Storage conditions: Name of manufacturer: Source of active pharmaceutical ingredient:			
Date of commencement of stability study:							
		Time intervals (Months)					
Specification	Limit	0	3	6	9	12	24

c) **DISCUSSION AND CONCLUSION OF SHELF-LIFE FOR EACH TYPE OF CONTAINER**

VMRF 1

PART 2 H PHARMACEUTICAL DEVELOPMENT

a) Highlight and motivate any differences in formulation and/or method of manufacturing of the different batches used in stability, bioequivalence and clinical studies.

b) Pharmaceutical Expert Report

i) Active Pharmaceutical Ingredient(s):

ii) Formulation:

iii) Production/Manufacture:

iv) Stability:

v) Conclusion of Expert Report:

vi) Name, signature and date of the responsible person:

vii) Reference list used in the compilation of the report:

VMRF 1

PART 2 I EXPERTISE AND PREMISES USED FOR MANUFACTURING OF VETERINARY BIOLOGICALS

1. **DETAILS RELATING TO THE PREMISES WHERE PRIMARY PRODUCTION IS UNDERTAKEN AND THE STAFF INVOLVED IN THE PRODUCTION AND TESTING OF VETERINARY BIOLOGICALS.**

   a) Description of the premises where all procedures involved in the preparation of the primary production or bulk batch is carried out. (A floor plan must be included):

   b) Details of other purposes for which the premises are used:

   c) Names, qualifications and field and duration of experience of the persons responsible for the manufacture, testing and release of the veterinary biological medicine, in the form of the primary production or bulk lot and the final containers ready for sale:

2. **NAME AND ADDRESS OF FACILITY WHERE THE IMPORTED FINAL FILLING LOT IS STORED**

VMRF 1

PART 3 BIOEQUIVALENCE AND BIOAVAILABILTY

a) STATE THE PURPOSE OF THE STUDY

(i) As comparison of formulation to be marketed versus formulation used in clinical trials, or
(ii) As proof of efficacy for a multi - source application, or
(iii) As proof of efficacy of new formulation (formulation change)

(b) REFERENCE PRODUCT USED

(i) Clinical trial formulation
(ii) Innovator product
(iii) Current formulation (for change of formulation)

The following must be indicated:

	Reference product	Formulation applied for
Name of product		
Batch no		
Holder of certificate of registration		
Country where purchased		
Assay results		
Source of API		

(c) METHOD USED

Describe the method in full, e.g. bioavailability, dissolution, etc.

(d) VALIDATION

Validation data for all quantitative assay methods shall be included.

(e) STUDIES

Include protocol , final report , assay validation report , pharmacokinetic report (including individual animal data) and statistical report.

(f) DISCUSSION AND CONCLUSION

Attach documents (where applicable)

VMRF 1

PART 4 PRE-CLINICAL STUDIES

a) Pre-clinical Expert Report

b) The following are Parts obtained and conclusions drawn from tests performed pre-clinically to demonstrate all aspects of the toxicity of the medicine, and to prove the safety of its use, with special reference to -

(i) acute toxicity,
(ii) subacute toxicity studies;
(iii) chronic toxicity studies;
(iv) reproduction toxicity and teratogenicity studies;
(v) carcinogenicity studies;
(vi) mutagenicity studies; or
(vii) environmental impact studies for veterinary medicines
(viii) pharmacokinetics studies:
(ix) neurological studies
(x) other tests to substantiate the safety of the veterinary medicine;

c) The following are Parts obtained and conclusions drawn from tests performed pre – clinically to demonstrate all aspects of the efficacy of the veterinary medicine , with special reference to ;

(i) The methods and experimental results of and the conclusions drawn from tests performed pre-clinically with reference to the efficacy of the veterinary medicine;
(ii) the relationship between the tests performed and the purpose for which the veterinary medicine is or will be used, or for which it will be propagated, and
(iii) the dosage and method of administration of the veterinary medicine, are as follows:

In cases of multi – source products, the MCC may grant exemption from the submission of some or all of the above information.

VMRF 1

PART 5 SAFETY AND EFFICACY

a) Expert Report

b) The field trials performed on target species with regard to the safety of the use of the veterinary medicine, with special reference to the particular dosage, routes of administration used and the side-effects observed,

c) Particulars of clinical or field trials conducted to establish the efficacy of the use of the veterinary medicine ,

d) Experimental details and results of the studies performed to establish the correlation between the applicable blood and other suitable physiological concentrations and the pharmacological action claimed for the veterinary medicine are as follows:

e) Veterinary medicines for food – producing animals : Residue depletion studies and recommended withdrawal periods

In cases of multi – source products , the Council may grant exemption from the submission of some or all of the above information as laid down in the guidelines for the registration of these products.

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

GUIDELINE FOR APPLICATIONS TO AMEND THE REGISTRATION DOSSIER OF A MEDICINE

This document has been prepared to serve as a recommendation to the holder of a certificate of registrations wishing to submit applications for amendment of registration dossiers of medicines. It represents the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. Applicants should note that there are major changes in the mannerin which amendments will be handled in future as described in this document.

REGISTRAR OF MEDICINES
MS M. P. MATSOSO
DATE: 30-05-2003

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AMENDMENTS

1. INTRODUCTION

This document has been prepared to guide holder of a certificate of registration when making amendments to registered medicines. It is acknowledged that the holder of a certificate of registration may make amendments from time to time with the aim to improve safety, quality and efficacy of a medicine or to improve product information. It is, therefore, the objective of the MCC to process the amendments as quickly as possible, hence, this policy document has been prepared to be used as a tool to address all matters concerning amendments

Amendments to the registration dossier are necessary to maintain the safety, quality and efficacy of a medicine and to ensure compliance with current technical requirements and to adhere to administrative aspects, and to keep abreast of scientific progress, or to reflect new therapeutic indications.

This document is intended to changes in facilities (including change in the holder of certificate of registration), pharmaceutical and analytical aspects of the medicine. It is the responsibility of the holder of the certificate of registration to provide comprehensive documentation to support the amendment application and to comply with the conditions determined by Council.

2. APPLICATION FOR THE AMENDMENT TO A REGISTRATION DOSSIER OF A MEDICINE

2.1 Applications for amendments to existing dossiers must be submitted on the appropriate application form (MRF 3A or MRF 3B) and accompanied by a cover letter detailing the type of amendment required as described below.

2.2 **Incomplete submissions or submissions which do not comply with the requirements as described will not be evaluated. These must be collected within 14 working days, failing which such applications will be confiscated.**

2.3 An amendment application may not address more than one product unless the products constitute a range for which a single application for registration dossier was submitted at the time of application for registration. Further, unless it is an application for change of name or address of the holder of certificate of registration only, in which case details for a group of products may be submitted. However, each registration dossier must be updated in accordance with the change

2.4 All applications for amendments must be properly bound on the left side as this allows for easy update and addition of pages to the dossier. It is preferred that documents be bound with plastic ring binding or punched (2-hole) and secured. The use of lever-arch files and any kind of paper clip is not recommended.

2.5 The date of the covering letter must be reflected on every page of the submission letter in black.

2.6 All pages must be paginated and the document indexed according to the existing MRF 1 Parts (e.g. page 2B-1 referring to PART 2B, first page).

2.7 Include dividers or tabs where applicable for ease of locating sections in the document.

2.8 Submit the front page of the amended MRF 1 Parts and the amended pages only when amendments are made which involve updating of a limited number of pages.

2.9 When extensive updating of the dossier is done, **a completely updated dossier** must be submitted and the amended sections clearly indicated. It is not acceptable to submit selected pages only when a full update is submitted. Such full updates must preferably be bound with plastic ring binding or punched (2-hole) and secured. The use of lever-arch files or any kind of paper clip is not recommended.

2.10 All documents in a foreign language must be translated into English and certified or verified.

2.11 When an application for amendment is submitted, the ADMINISTRATIVE DATA of the MRF1 form must be updated with regard to C. UPDATE HISTORY. The date of application of each amendment (previous and current) for the last three amendments, summarised details of the amendment/s, and date of approval by the Medicines Control Council must be provided in tabulated format.

2.12 Amendments to applications for registration before registration are not permitted, unless advised by or negotiated with Council.

3. APPLICATION TO AMEND THE PARTICULARS REGARDING PROPRIETARY NAME, HOLDER OF CERTIFICATE OF REGISTRATION, MANUFACTURER, PACKER, FINAL PRODUCT RELEASE CONTROL AND FINAL PRODUCT RELEASE RESPONSIBILITY

3.1 GENERAL INFORMATION

3.1.1 Applications pertaining to the above must be submitted under cover of form MRF 3A.

3.1.2 Amendments must be accompanied by the appropriate amendment fee. If a cheque is submitted to cover the amendment fees for more that one product, a list of the products involved with the reference numbers and date of requesting the specific amendment for each product must be supplied. A copy of this letter as well as a copy of the cheque must be included in the application for each individual product.

3.1.3 Amendments to registered products must be accompanied by the original registration certificate. A copy of the registration certificate will not be accepted as the original must be replaced. Where the original certificate has already been submitted to Council, this must be indicated on the MRF 3A form. **(Original certificate already submitted with application dated ....., reference no. .....)**

3.1.4 All amendments must be accompanied by updated administrative details (front page) of the MRF 1 front page.

3.1.5 As the processing of these amendments results in the updating of the database and the issue of amended registration certificates, the holder of the certificate of registration must ensure that details with regard to previously approved facilities are updated to reflect

name and address changes of companies through the years. Changes must be detailed, and the appropriately amended Parts included in the submission.

3.1.6 Should there be a discrepancy between the administrative data submitted with the amendment request and the relevant Parts, the data in the Registration Dossier on file will be reflected on the registration certificate.

3.1.7 It is the responsibility of the holder of the certificate of registration to ensure that details with regard to the facilities / laboratories applied for are correctly reflected on the front page, and to check registration certificates for correctness and communicate discrepancies to Council within 30 days of receipt thereof.

3.1.8 If the holder of the certificate of registration is of the opinion that the information reflected on the registration certificate is incorrect, the holder of certificate of registration must provide the correct approved **information together with the letter(s) of approval by the Council**. An amended registration certificate will be issued free of charge should the error have occurred at this office.

3.1.9 A change can only be considered final once the holder of the certificate of registration has been supplied with the new registration certificate for registered medicines, or a final letter of approval of the amendment from the Council in the case of an old medicine.

3.1.10 Updating of dossier: If the dossier has not been updated during the previous 5 years, or an application for a major change is lodged, a fully updated dossier must accompany an application for transfer of the certificate of registration or change in manufacturer.

3.1.11 All relevant documentation must be submitted as one document and different Parts should not be submitted separately. Duplicate documents may not be submitted to different sections.

3.1.12 The processing of the request is not a mere formality. Each application has to be evaluated on an individual basis before such a request may be approved. The authorisation for change is dependent on various aspects including the proposed new holder of certificate of registration / manufacturer / packer / laboratory's infrastructure and its compliance with Good Manufacturing Practice in terms of the guidelines as recommended by the World Health Organisation and SA Guide to GMP.

3.1.13 In order to assess the suitability of the proposed holder of certificate of registration, manufacturer, packer or laboratory, an inspection by Council Inspectors may have to be performed prior to the authorisation of the change requested.

3.1.14 Please, note that once a change in HCR /manufacturer/packer/FPRC/FPRR has been approved, the updated pages to the Parts are placed on file. Subsequent updates of the dossier should not again indicate an application for change in these aspects.

3.2 CHANGE OF PROPRIETARY NAME

3.2.1 Application to change the proprietary name of a product must be submitted on an official letterhead of the HCR and the reason for the amendment must be clearly stated.

3.2.2 Changing of the proprietary name during the evaluation and registration phase will only be permitted if the Council has not accepted the name originally proposed by the applicant.

3.2.3 The HCR must be accompanied by an amended Administrative Section of MRF 1, Part 2B (Formulation) and the professional package insert and patient information leaflet.

3.2.4 The policy on change of proprietary names is detailed in the Guidelines for Registration of Medicines – General Information.

3.3 CHANGE OF HOLDER OF CERTIFICATE OF REGISTRATION

3.3.1 The proposed HCR must have submitted a Holder of the Certificate of Registration Master File HCRMF) prior to any application for transfer of a medicine registration certificate.

3.3.2 An application for a change of HCR must be submitted on a company letterhead under cover of MRF 3A together with the following documentation:

3.3.2.1 Details of the current holder of the certificate of registration
3.3.2.2 Details of all other companies involved in the manufacturing of this product.
3.3.2.3 Statement by holder of certificate of registration to confirm possession of master documents, existence of contracts, commitment to updating dossiers and detailing changes in the manufacturing process
3.3.2.4 Signed letter of cession by the current HCR on an official letterhead
3.3.2.5 Signed letter of acceptance by the proposed HCR on an official letterhead
3.3.2.6 The original registration certificate (registered products
3.3.2.7 The amendment fee
3.3.2.8 Updated administrative data (MRF 1 front page cover)
3.3.2.9 Inspection flow diagram for the product
3.3.2.10 Organogram of proposed HCR (including the names of key personnel with specific reference to production and quality assurance)

3.3.3 The letter of cession from the current legal HCR must confirm that the full application dossier (MFR 1) and product history have been transferred to the proposed HCR.

3.3.4 It should be noted that the final product release responsibility (FPRR) often changes when a registration certificate is transferred. The application for registration dossier must be appropriately updated to reflect this change. (Front page cover). This change must be clearly indicated.

3.3.5 The Registration dossier must be fully updated to the current statutory format and current scientific standards within 12 months after transfer of the registration certificate. In the case of mergers the HCR must adhere to the programme of updating of dossiers as approved by the Council. The date by which the dossier will be fully updated must be clearly reflected in the covering letter.

However, if the dossier had not been updated during the previous 5-year period, a fully updated dossier must accompany the application for transfer of the registration certificate.

3.3.6 The proposed HCR must ensure that the registration dossier presented to them has been fully updated recently (at least during the last 5 years) and that the full product history is provided by the current HCR.

3.3.7 An holder of certificate of registration must be in possession of all specifications relevant to a product

3.3.8 The current HCR remains legally responsible and liable until transfer of the registration certificate has been confirmed in writing.

3.4 CHANGE OF / ADDITIONAL: MANUFACTURER, PACKER/ FPRC/FPRR

3.4.1 An application for change of manufacturer/packer/FPRC/FPRR must be submitted on an official company letter head under cover of form MRF 3A

3.4.2The following documentation must be included:

3.4.2.1 Details of holder of certificate of registration

3.4.2.2 Details of all other companies involved in manufacturing of the product

3.4.2.3 Statement by holder of certificate of registration confirming possession of master documents, existence of contracts, committing to updating of dossiers and detailing changes in the manufacturing process

3.4.2.4 Inspection flow diagram for the product

3.4.2.5 The original registration certificate (registered products)

3.4.2.6 The amendment fee

3.4.2.7 Updated administrative data MRF 3

3.4.3 The following data pertaining to manufacturing/packing/laboratory sites (local and overseas) will be required.

- Site Master File if not previously submitted
- Organogram listing all the key personnel

3.4.4 For manufacturers/packers outside the borders of South Africa the following additional information will be required:

3.4.4.1Copy of the latest inspection report-

3.4.4.2 For a recognised country with a competent regulatory authority, a GMP certificate of compliance in terms of WHO Certification Scheme or a GMP certificate issued by a competent authority for the manufacturing site or copy of the manufacturing licence (not older than 2 years) will be sufficient.

3.4.4.3 For manufacturers in "non-recognised" countries, that haven not been inspected by a recognised authority, an inspection report from a recognised authority will be required.

OR

3.4.4.4 For manufacturers in "non-recognised" countries that have not been inspected by a recognised authority, an inspection by Council Inspectors may be required.

3.4.4.5 For change in manufacturer:

3.4.4.5.1 Where the manufacturing procedure (including equipment) is identical to the manufacturing procedure currently used, the following mustbe submitted:

i) a statement signed by the managing director (or in the case of an overseas country the head of the production plant or chief technical

officer) that the manufacturing procedures and equipment are the same as that currently used;

ii) updated Front Page

iii) *However, if the dossier had not been updated during the previous 5-year period a fully updated dossier must accompany the application for change of, or for an additional, manufacturer.*

3.4.4.5.2 Where the manufacturing procedure (including equipment) differs, but falls within the minor Type A of Type B amendments, the following must be submitted:

i) a statement signed by the managing director (or in case of an overseas country, the head of the production plant or chief technical officer) that the changes to the manufacturing procedures fall within the Type A ot Type B amendments;

ii) updated Parts according to the prescribed format. The changes in the manufacturing process must be clearly stated to facilitate evaluation
PART 2E
PART 2C where relevant.
- Other amendments falling within the Type A or Type B changes.

iii) *However, if the dossier had not been updated during the previous 5-year period, a fully updated dossier must accompany the application for change of, or additional, manufacturer.*

3.4.4.5.3 For an alternative or additional manufacturer where the manufacturing procedure (or equipment) is different from the manufacturing procedure (or equipment) currently on file falling out of the Type A or Type B amendments, the following must be submitted:

i) Changes to PARTS in prescribed format. The changes in the manufacturing process must be detailed to facilitate evaluation

ii) A fully updated dossier.

iii) details of the proposed validation programme to be followed for at least the first three production batches.

iv) stabililty data and comparative efficacy data as required for Type C amendments

AMENDMENTS

Note: Major deviations: sale of product may only commence after written approval had been granted by the Council. When such batches are manufactured, all documents and bulk and/ or intermediate stock should be clearly marked as being "validation batches".

3.4.4.6 Change in packer

- Statement confirming that the packing process is unchanged

or

- Updated PART 2E and Part 2D (where relevant) in prescribed format. The changes in the packing process must be detailed to facilitate evaluation.

3.4.4.7 Change of final product release laboratory of final product release responsibility

- Updated Administration Front Page.

3.4.4.8 Holder of certificate of registrations should study the requirements in the SA Guide to GMP.

Attention is particularly invited to the following from the GMP Guide:
12.2.1 A Contract Giver should assure himself that the Contract Acceptor has adequate premises, equipment, and staff with sufficient knowledge and experience, to carry out satisfactorily the work placed with him. In order to do this, the Contract Giver should audit the Contractor Acceptor's premises, equipment and systems both before the contract is given and at regular intervals thereafter. Audit reports should be issued and kept on record. A Contract Giver may only use the contract manufacturer or packer as approved in the registration dossier.

5.4.4.9 The HCR is advised to discuss the latest Council inspection report of the proposed contract giver with the contract acceptor prior to entering into an agreement with the contract giver.

3.4.4.10 In the case of contract packaging by a third party, the relevant cGMP requirements should be adhered to.

3.5 CHANGE OF NAME OF HOLDER OF CERTIFICATE OF REGISTRATION ONLY

3.5.1 In this case application to change the name of the holder of certificate of registration may be submitted for a whole range of products. Old medicines and registered products must be dealt with under separate cover.

3.5.2 The application for change of name of holder of certificate of registration must be submitted on an official letter head under cover of MRF 3A

3.5.3 The updated HCRMF, updated organogram of the proposed HCR, copies of the registration certificates (IPCSA and Registrar of Companies) as well as copies of the old and new company letterheads must be submitted.

3.5.4 In alpha-numerical order according to application number of the product:

3.5.4.1 The registration certificate of each product (for registered products)
3.5.4.2 Updated front page
3.5.4.3 Updated front page to reflect the name change only of the FPRR, if the holder of certificate of registration is also the FPRR.
3.5.4.4 Amendment fee

3.6 CHANGE OF ADDRESS OF HOLDER OF CERTIFICATE OF REGISTRATION

3.6.1 In the case of a change in address of a HCR, the HCRMF has to be updated.

3.6.2 The front page of the Registration dossier for each product must be updated during the first subsequent update of the dossier.

3.6.3 A separate letter addressed to DATA CONTROL section must be submitted reflecting details of the change of the HCR's address to ensure the updating of all lists.

3.6.4 However, if the HCR is also the FPRR, the requirement for change of holder of certificate of registration will apply as this will result in a changed in the registration certificate.

3.7 CHANGE OF ADDRESS OF HOLDER OF CERTIFICATE OF REGISTRATION / MANUFACTURER / PACKER / LABORATORY

3.7.1 In the case of any of the above, the following has to be provided:

3.7.1.1 Updated SMF
3.7.1.2 Organogram of the proposed holder of certificate of registration (including the names of key personnel with specific reference to production and quality assurance departments)
3.7.1.3 The relevant amendment fee
3.7.1.4 The original registration certificate
3.7.1.5 An updated front page reflecting the name and address of manufacturer(s), packer(s), FPRC and FPRR
3.7.1.6 Updated Parts, as relevant, in the prescribed format

4 AMENDMENTS TO THE PHARMACEUTICAL AND ANALYTICAL ASPECTS OF REGISTERED MEDICINES

4.1 INTRODUCTION

This information is for amendment of a registration dossier already lodged with the medicines control council, pertaining to parts 2 (Part 2A through to Part 2I) of the application registration dossier (The active ingredient, formulation, active and inactive pharmaceutical ingredients, specifications and procedures; manufacturing and packaging procedures; in-process and final

product specifications and control procedures: container specifications and control methods; stability and shelf-life of the product).

It is practically difficult, if not impossible, to review all pharmaceutical amendments to every pharmaceutical product in registered by Council. This document is also aimed at trying not to prejudice the HCR in terms of medicine regulation. It is also the responsibility of the HCR to comply with the requirements of this policy document and all other policies.

Full updates should be done according to a plan and program designed in consultation with the HCR. Otherwise, full updates should only be made on product registration review date (at five year intervals).

In all cases the HCR should record and report on all types of amendment that have been applied for or that have been implemented. Council Inspectors may also audit such changes during an inspection carried out for whatever reason. No amendments that require prior approval should be implemented without due written approval by Council. Contravention of this provision will result in Council taking severe steps against all defaulters.

Notification should be 30 days prior to implementation date. If this is not practical, notification should be not be later than a month after implementation.

It should be noted that these guidelines may be applied to all dosage forms including parenterals where specifically indicated.

4.2 GENERAL INFORMATION

4.2.1 Applications pertaining to the amendments described in 4.1 above must be submitted under cover of the MRF 3B.

4.2.2 The general information under 5.1 applies to these applications.

4.2.3 All submissions with regard to amendments to existing MFR1 as well as reply to Council Resolutions must be accompanied by a covering letter in the format indicated in

4.2.3.1 All differences between the current and the amended PARTS must be reflected in detail in the covering letter. The reasons for the changes must be clearly and succinctly stated. Vague statements like "General Update" and "MCC Policy" are meaningless. The changes requested must be stated explicitly.

4.2.4 When answering a letter from the Registrar of Medicines, a copy of the relevant letter must be included in the response and the reply cross-referenced to the actual questions raised.

4.2.5 In case of a general change in the manufacturer of an active raw material, or in raw material specification, where more than one product (same dosage form) is affected, the updated PARTS of the products involved can be submitted only upon approval of the general changes.

Example: For an additional supplier of active raw material, the additional supplier should be first approved for one product and then all the relevant **PART**

2A's of the various products involved updated. A copy of the letter of approval of the first product must be included in the subsequent updates.

4.2.6 Where extension of the shelf-life of a product is requested, SUPPORTING STABILITY DATA MUST BE SUBMITTED.

4.3.6.1 An indication of the requested shelf-life must be included.
4.3.6.2 Stability data sheets must state the specification limits of parameters as reflected in PART 2F
4.3.6.3 Stability data should ideally be submitted in tabulated format according to the specifications in PART 2 F (same sequence).

4.2.7 Four different types of amendments can be identified:

4.2.7.1 Type A - that can be implemented without intervention of or notification to the authority
4.2.7.2 Type B - that require only notification*,
4.2.7.3 Type *C* - that require prior approval*
4.2.7.4 Type *D* - that should be considered to be new applications*.
*For the conditions that apply refer to tables below.

Note: Type A and Type B amendments must be recorded and reflected under MFR 1 – Administrative data – C. UPDATE HISTORY with the next Type C application.

4.3 ONCE-OFF CHANGES (DEVIATIONS) DURING MANUFACTURE

In the event of a once-off formulation or manufacturing procedure change the holder of certificate of registration must refer the application to **Council Inspectors** and receive written confirmation before proceeding to release the batch.

4.4 TYPES OF PHARMACEUTICAL AND ANALYTICAL AMENDMENTS AND PROCEDURES TO BE FOLLOWED.

The process is only valid if the correct procedure is followed, the conditions, if any, are met, and the required documents are submitted. Data or a commitment to generate stability data must be provided where relevant.

It is the holder of certificate of registration's responsibility to ensure that any amendment made does not in anyway negatively affect the quality, safety and efficacy of the medicine. Should any doubt exist, prior written authorization should be obtained.

It should be noted that the Medicines Control Council (MCC) retains the right to withdraw any concession granted to an holder of certificate of registration by virtue of the provisions of this Guideline, should the holder of certificate of registration's manufacturing facility not comply with current Good Manufacturing Practice (cGMP) as determined by the MCC.

Furthermore, suitably authorized amended master documents should be prepared prior to the manufacture of such medicine.

The holder of certificate of registration must undertake to ensure that the stability of the relevant product is established and that validation and qualification procedures are instituted in order to ensure that the quality, safety and efficacy of the original product has not been affected by these amendments.

The holder of certificate of registration must ensure that, in the case of solid oral dosage forms, the acceptance criteria for dissolution rate on release characteristics comply with the current specification for the product. These studies must be performed in accordance with current guidelines wherever required prior to implementation of changes.

Data to demonstrate efficacy and or stability must be derived from batches of at least 100 000 tablets or capsules. For semi-solid dosage forms batch sizes greater than 100 kg are to be used.

NB: Only relevant data in support of the proposed changes/amendments should be submitted together with the reasons for submitting such data

4.4.1 Type A - Amendments that do not require prior approval and that can be implemented without involvement of the MCC

The holder of certificate of registration should have a standard operating procedure whereby amendments are recorded and available for inspection by the MCC. At any point where amendments are submitted to MCC – all Type A amendments should be included in the MFR 1 - Administration Data - section C. (Update History). For Type A amendments see Table 1 below.

4.4.1.1 The following general conditions should be complied with whenever Type A and/or Type B amendments are made:

Type B should not made with amendments that require prior approval

4.4.1.1.1 Amendments can only be made to registered products or "Old medicines"

4.4.1.1.2 Date of implementation of Type B amendment should be indicated

4.4.1.1.3 If the M.C.C request copies of experimental validation data, these should be supplied within 30 days of the request and they are made available during GMP inspections

4.4.1.1.4 Specific conditions relating to the amendment are complied with.

4.4.1.1.5 All M.C.C standards are complied with.

4.4.1.1.6 Type B amendments are always accompanied by a statement that no amendments have been made to the product other than those specified in the notification.

4.4.2 Type B – Amendments that require only notification.

The appropriately amended Annexures affected by the change must **be submitted** and be **accompanied or followed by** stability data as indicated in the attached table. Written notification of the type of amendment must **then** be forwarded to this office **30 days** prior to **implementation**. The notification must be clearly marked "Type B amendment" (see Table 1 below) **and must outline (a) the nature of the change with the relevant code, (b) the category number of the applicable item in the table below, (c) the affected and amended Parts / Annexures of the MRF1 / MBR1 dossier, (d) any supportive information and/or data, and (e) any applicable documentation included in the above-mentioned submission.**

Where a site change for manufacturing or packaging is concerned, confirmation of the positive GMP status of the new site must be obtained in writing from the inspectorate before implementation.

4.4.3 Type C - Amendments that require prior approval:

The appropriately amended Annexures / Parts affected by the change must be submitted together with the relevant data/documentation. The submission must be clearly marked: "Type C amendment" (see Table 3). Written approval from the MCC must be obtained before the change may be implemented.

4.4.4 Type D- Amendments that should be considered to be new applications

4.4.4.1 Change in the active pharmaceutical ingredient (API) to a different API

4.4.4.2 Inclusion of an additional API, or removal of one API from multi-component product

4.4.4.3 Change in the dose of one or more of the API

4.4.4.4 Change in the dosage including: change from an immediate –release product to modified-release dosage form or vice versa and change form liquid to powder for reconstitution, or vice versa

4.4.4.5 A change in the route of administration

NB: For amendments not covered by this document and/or where the specified conditions are not complied with, the normal data requirements apply and prior approval must be obtained.