MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

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SAFETY OF VETERINARY BIOLOGICALS

This guideline has been prepared to serve as a recommendation to applicants wishing to submit data as evidence of safety for veterinary biologicals. It represents the Medicines Control Council's current thinking on this topic. It is not intended as an exclusive approach and 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 and in doing so reserves the right to make amendments in keeping with the knowledge which is current at the time of consideration of data for safety of veterinary medicines.

REGISTRAR OF MEDICINES
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CONTENTS :

1 .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 seroconversion 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.

2.(a) 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 employed during 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:

(i) 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

(ii) 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

(iii) 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

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

(v) 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)

(b) SPECIFIC SAFETY DATA:

The following data is required:

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

(ii) 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

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

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

(v) 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*

(vi) 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 fish, other aquatic species or reptiles.

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.

(vii) 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 large 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 methods and recording methods. Field safety tests could be combined with field efficacy tests.

(viii) 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.

(ix) 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/titers
(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

(x) 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 authorization 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 authorization, 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.

(c) ADDITIONAL SAFETY DATA:

(i) Examination of reproductive functions:

Safety data is not required if the product is not indicated for use in animals of a reproductive age

(ii) Examination of immunological functions:

Safety data is 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

(iii) Spread of the vaccine strain:

Data has 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.

(iv) Data has 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

(v) Dissemination in the vaccinated animal:

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

(vi) Reversion to virulence:

In the case of a virus vaccine:
Data has 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.

(vii) Recombination or genomic reassortment:

An evaluation of the possibility of recombination or genomic reassortment should be submitted.

(viii) 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.

(ix) Interactions:

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

3. 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.

4 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 do 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 characterization of the DNA segments added or deleted, as well as a phenotypic characterization 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 a 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 immunizing antigens. Live vectors may carry one or more foreign genes that have been shown to be effective for immunizing target host animals.

5. 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.