MEDICINES CONTROL COUNCIL

EFFICACY OF VETERINARY BIOLOGICALS

This guideline has been prepared to serve as a recommendation to applicants wishing to submit data as evidence of efficacy 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 efficacy of veterinary medicines.

REGISTRAR OF MEDICINES
MS M.P. MATSOSO

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PURPOSE

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 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 husbandry practices in the country.
An evaluation of efficacy will also be done in light of the specific strains of organism(s) that are present in the country.

(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 labels.

1. 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:

1.1 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

1.2 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

1.3 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

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

1.5 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)

2. SPECIFIC EFFICACY DATA:

The following data is required:

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

2.2 Proof of the efficacy of the product with the exact composition as stated in I(1)(d). This would include the specific strain of virus or bacterium, 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*

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

2.4 Proof of the efficacy of the exact product to be registered for each species on the label.*

2.5 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*

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

2.7 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

(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 virus/bacterium 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 of bacterium/virus is not required.

2.8 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

2.9 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.

2.10 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.

3 ADDITIONAL EFFICACY DATA

3.1 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 dessicated live vaccine, proof must be submitted that there is no bacteriocidal 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.

4. REFERENCES:

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

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

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