GUIDELINES ON

DEMONSTRATION OF EFFICACY OF ECTOPARASITICIDES DURING CONDUCT OF ECTOPARASITICIDE TRIALS IN UGANDA

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Authorization of these guidelines

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ABBREVIATIONS AND ACRONYMS

LTR: Local Technical Representative

MAAIF: Ministry of Agriculture, Animal industry and Fisheries

NDA: National Drug Authority

1.0 Objective

This document is intended to provide special guidance on the general requirements for the assessment of efficacy of an ectoparasiticide preparation, containing novel or established active ingredients in Uganda.

2.0 Scope

The guidelines relate to ectoparasiticides for application to animals for control of Ectoparasites in Uganda.

3.0 Policy

3.1 Section 35 of the National drug Policy and Authority Act empowers NDA to scientifically examine any drug for purposes of ascertaining efficacy, safety and quality of the drug and that it may institute a system for the approval of the drug or drug combinations not included on the national lists of essential drugs.

3.2 Section 40 of the Act mandates NDA to issue a certificate to any person for purposes of carrying out clinical trials, in this respect to ectoparasiticide field trials that may be specified in the certificate.

3.3 The National Drug Policy and Authority (conduct of ectoparasiticides field trials) Regulations, 2014, statutory instrument No.30:

a) Regulation 3(1) of provides that, subject to this regulation field trials shall be conducted for ectoparasiticides that are registered under the Act and for ectoparasiticides that are not registered under the Act, prior to the ectoparasiticides being supplied, administered or used.

b) Regulation 3(3) provides that where a field trial is for an ectoparasiticide that is not registered by the Authority under the Act, the field trial shall be conducted to ascertain- The effectiveness and safety of the ectoparasiticide in animals, The safety of the ectoparasiticide to humans, the safety of the ectoparasiticide to the environment and any other factor, as may be deemed necessary by the Authority.

c) Regulation 3(3) requires that a field trial shall be conducted for a period of at least six months.

d) Regulation 4 requires that a person shall not start or cause to be started a field trial or conduct a field trial, without the authorisation of the Authorit.

4.0 Distribution

1.0 Secretary to the Authority, NDA

1.1 Contracted Research Organisation(CROs)

1.2 Sponsors of clinical/ field trails

1.3 NDA website.

1.4 Shared folder for all staff on NDA on head office server (\\ndaserver\qms\guidelines).

1.5 Shared folder for all staff on NDA laboratory server (\\ndqsvr\qms\guidelines).

5.0 General requirements

a) The purpose of treatment with ectoparasiticides is to eliminate or to reduce ecto parasites or to protect animals from the parasites, in order to maintain animal health and to prevent losses in production.

b) Ectoparasiticides intended for external use will have to fulfill the Authority`s requirements for approval of veterinary medicinal products.

c) While in principle, the results of dose titration and dose confirmation trials are acceptable irrespective of where they are carried out, the Authority requires additional clinical field trials to be undertaken to scientifically assess the efficacy of the ectoparasiticides. This assessment is undertaken because animal husbandry or environmental conditions differ markedly from the reported test conditions.

d) To establish the clinical efficacy of an ectoparasiticide product, the following test phases are recommended:

(i) Description of the mode of action
(ii) Titration of dose
(iii) Dose confirmation trials
(iv) Clinical field trials

e) The test phases will usually be based on the results of preliminary in vitro studies using the target ectoparasite(s) claimed, i.e. studies on the potential spectrum of activity and the prospective dose.

5.1 Mode of action

a) The pharmacodynamics of the active ingredient(s) on the target ectoparasite(s) should be adequately described in terms of the sequence, speed and intensity of the various effects; replicates should be included. Approximate effective concentrations should be indicated.

b) Where applicable, the influence of temperature on the efficacy of the product should be evaluated.

c) Where applicable, the influence of excipients should be described.

d) In evaluating the results of in vitro tests, the ABBOT formulashould preferably be used, i.e. if the mortality rate of untreated control arthropods exceeds 20%, the test results cannot be utilized in the assessment of efficacy of the proposed product.

e) The pharmacokinetics and pharmacodynamics of the product in the target animal species should be described, whenever it is applicable.

5.2 Clinical field trials

a) Clinical field trials are required primarily for follow-up evaluation of the performance of the product as employed by the user in the field and to gain experience on the efficacy and safety of the product when applied under various clinical conditions.

b) Field trials should be conducted in at least 2 different geographic and climatic regions, where appropriate. The habitats and the prevalence of ectoparasite species must be described.

c) The Authority requires additional regional field trials depending on husbandry practices, environmental conditions and resistance profile of ectoparasites where scientifically justified.

d) Data on a sufficient number of treated animals are required. When treatment of groups is intended, preferably 25-50% of the groups under trial should be left untreated. Where this cannot be justified, 25-50% of the groups should be treated with an established product (registered) which is indicated for control of the ectoparasite or groups of ectoparasites claimed. In exceptional cases, where justified, studies may be performed without the use of control animals (e.g. in the case of animals infected with Sarcoptes scabiei). When treatment of individual animals is intended, more specifically small companion animals, studies without the use of control may be performed if justified.

e) Efficacy may be determined by counting of ectoparasites on the animal, or, where this is not possible, by estimation (e.g. fleas). The choice of sampling times should be justified, e.g. in respect to the seasonal or daily time of a maximum infestation with ectoparasites, taking into account sites of predilection of the parasites. To minimize variations in the response, clinical trials should preferably be performed in animals of the same breed.

However, efficacy must be demonstrated in different breeds representing the target population. All procedures should be described and validated or should be based on published methods which must be cited. The investigator should use the same technique throughout the trial.

f) Where applicable, groups of treated and control animals should be established by random selection.

g) Parasite related diseases should be described before initiation of treatment and the regression of clinical symptoms and the cure of diseases respectively should be monitored during the study period.

h) A statistical analysis of the results of each trial as well as the overall efficacy of the product should be conducted, where appropriate, for each arthropod species claimed.

i) The animals under trial should be observed at appropriate intervals during and after treatment, to record all adverse reactions and side effects.

5.3 Dose confirmation trials

a) At least two controlled tests are recommended to demonstrate the efficacy of a new product against each ectoparasite species and stage of development as indicated in the labeling.

b) Where applicable, trials should be performed in different geographic and climatic regions.

c) Where applicable, at least one trial should be performed using naturally infested animals.

d) Statistically adequate numbers of treated and control animals are necessary for each trial. The applicant must justify treatment group sizes.

e) Trials should be conducted using the formulation intended for marketing and using the recommended dose and administration techniques.

f) When efficacy is claimed for parasites in which resistant strains have emerged and the product is likely to be used in animals exposed to resistant strains, a controlled trial using recognized scientific techniques will be necessary to establish efficacy, if the new active ingredient has: a similar mode of action to that of the existing ectoparasiticide; a close chemical analogy to that of the existing ectoparasiticide should be demonstrated.

5.4 Titration of dose

a) The purpose of the trials is a determination of the effective dose to be recommended. Ideally the final formulation should be used in these trials. In exceptional cases, where justified, an equivalent formulation may be used.

b) The efficacy of the product should be evaluated using appropriate tests. A use of the controlled test is recommended (see Appendix I).

c) The parasite species chosen for titration of dose studies should be evaluated in relation to the indications for the product. Naturally infested or, where applicable, artificially infested animals can be used.

d) Ideally, four groups, each consisting of a sufficient number of animals to allow statistical analysis, should be administered 0, 0.5, 1 and 2 times the anticipated recommended dose. Each group should harbor or be uniformly infested with adequate numbers of each species of ectoparasites. Single or mixed infestation may be used.

e) e) Groups should be held under the same experimental conditions. Husbandry practices should be described.

f) The route and technique of administration should be the same as proposed for marketing.

g) The time intervals for ectoparasite counts should be justified, especially with regard to the biology of the ectoparasite(s).

h) Data obtained for each ectoparasite at the recommended dose in the dose titration trial(s) will be acceptable as one of the dose confirmation trials provided that:

(i) The formulation used was equivalent to the formulation intended for marketing,
(ii) The product was applied according to the labeling,
(iii) Adequate infestation of ectoparasite species was established
(iv) The number of test animals was adequate.

i) Product for topical use, e.g. exhibiting a direct knock-down, repellent or killing effect (non-systemic action): The evaluation of the anticipated recommended dose or concentration can be based, where applicable, on the results of appropriate preclinical tests including in vitro tests using isolated ectoparasite species indicated in the labeling (ED50, ED90, ED95, ED99, EC50, EC90, EC95, EC99 etc.).

6.0 Special requirements

6.1 Products for topical use

Products for topical use include shampoos, aerosols, spot-on, pour-on or dust formulations, ear tags, collars, clips, dipping or spray-race formulations, etc.

While the general requirements also apply to products for topical use, it is necessary to take into account interactions between treatment and regional climatic conditions during the course of the trial. In particular, the applicant should consider the need for additional studies as follows:

a) the effect of (artificial) rainfall at various intervals before, during and after treatment;

b) the effect of sunshine and hot weather under monitored conditions during and after treatment;

c) the effect of dilution factors with dipping;

d) the effect of washing and bathing during the treatment period;

e) the effects of hair length and thickness of coat;

f) the effect of dirtiness of animal coat and the effect of dirtying of preparations (e.g. of dipping formulations) during the treatment of groups;

g) the effect of self-grooming or mutual grooming of treated animals;

h) different body sizes of target animals treated with a standard dose formulation;

i) effects on the quality of fleece or hide and impact on tanning or processing.

Ideally, side effects and adverse effects of the product should be monitored during the trial and for several days afterwards. Where secondary pharmacodynamic effects are seen, a study on the dose/effect relationship may be required.

6.2 Insecticide-delivery systems (e.g. collars, ear tags etc.)

a) If the applicant claims that the product will be effective for a seasonal period of pest activity, then the trial must be conducted over the entire season.

b) Evaluation will be based on efficacy in controlling infestation with pests at the time stated by comparison with control animals, where relevant.

c) Controls and treated animals should occupy separate lots within the same area throughout the trial. Groups of animals should be maintained under such conditions to guarantee comparable parasite loads, but exclude interference between treatments and controls.

7.0 Demonstration of Efficacy

7.1 Minimum efficacy to support claims

Where a claim for control of infestation is made, the period of time it takes to achieve control and the period over which control is achieved must be demonstrated.

At the end of the trial period as indicated by the applicant, the overall efficacy of ectoparasiticides in treating infections in domestic animals should be achieved as follows:

a) for fleas: approximately 100%
b) for lice: approximately 100%
c) for mites: approximately 100% for Sarcoptes scabiei and, if possible, more than 90% for other mange mites
d) for ticks: more than 90%
e) for diptera: 80-100% (preferably more than 90%)
f) for larval arthropods: 80-100% (preferably more than 90%)

Where indicated and justified, clinical parameters may be used to support the efficacy of a product.

Where efficacy is less than the above, no claim should be made unless the applicant can demonstrate that the degree of efficacy achieved is better than or comparable with current alternatives.

All claims for efficacy of the product against particular species of ectoparasites must be validated.

7.2 Other considerations

In the design of efficacy studies, the following must be taken into account:

a) The kind of effect(s) exerted by the active ingredient(s) (e.g. flushing out, repellent, killing, anti-feeding or detaching effect, insect growth regulating effect, larvicidal, ovicidal, adulticidal or pupicidal effect);

b) Occurrence and susceptibility of ectoparasites in different geographic and climatic regions;

c) Control of ectoparasite-related diseases if indicated;

d) Safety of the target animals;

e) Pharmacokinetic behaviour of the substance under investigation;

f) Data on drug resistance of ectoparasite species, where available;

g) Products intended for the treatment of ectoparasitic conditions may affect the environment, etc. Therefore, due regard should be given in respect of operator, consumer and environmental safety.

h) For fixed combination products containing two or more active ingredients, it will be necessary to assess the potential advantages in the control of ectoparasites against possible disadvantages (e.g. synergistic or additive actions; antagonism; substitution of effects; non-effect (overkill), taking into account the guidance on Fixed Combination Products.

8.0 References

a) The National Drug Policy and Authority Act, (Cap 206 of 2000)

b) The National Drug Policy and Authority (Conduct of Ectoparasiticide field trials) regulations, 2014

c) National Drug Authority conduct of ectoparasiticide guidelines.Doc.No DID/GDL/003

d) Good Clinical Practice for the Conduct of Clinical Trials on Veterinary Medicinal Products (VICH – guideline, 2000).

e) Guidelines for Demonstration of Efficacy of Ectoparasiticides- Directive 81/852/EEC as amended.

9.0 Appendices

Appendix I

The Controlled Test

1. The efficacy of an ectoparasiticide can be determined by comparing the number of ectoparasites in the control animals with the number of ectoparasites in the treated animals after a suitable post treatment interval.

2. The population of infested animals should be randomly separated into at least two groups. The method of separating animals into groups must be described and justified. The first group serves as a control group while the other group(s) should be treated with the test product. After suitable time interval(s), ectoparasites should be recovered, identified and quantified with an appropriate method, where possible.

3. When a controlled field trial against temporarily infesting ectoparasite species is indicated, the population of animals should be randomly separated into two groups and placed on similar pastures. Groups of animals should be maintained under such conditions to guarantee comparable parasite loads, but exclude interference between treated animals and controls. Before start of treatment, it must be ensured that the ectoparasite burden is comparable in both control and treatment groups.

4. The percentage efficacy for each species of ectoparasites is determined by comparing the treated group and control group using the following formula:

   C –T/C x100 = % efficacy

   Where C = mean of the controlled group.

   T = mean of the treated group.

5. The mean may be the arithmetic mean, the geometric (i.e. logarithmic) mean or other suitably transformed mean. However, such transformation must be justified.

6. Results must be statistically analyzed and, where possible, confidence limits of the means should be given. The statistical method used must be justified.

10.0 Document Revision History

Date of revision	Revision number	Document Number	Author(s)	Changes made and/or reasons for revision
14/03/2017	0	DID/GDL/031	Jeanne	First Issue

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