PERFORMANCE ENHANCERS

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Additional Notes	The objective of this document is to provide specific guidance in relation to the documentation of the efficacy of performance enhancers, and should be applied in conjunction with Directive 81/852/EEC as amended, and the note for guidance on *Good Clinical Practice for the Conduct of Clinical Trials on Veterinary Medicinal Products in the European Union.*

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1. INTRODUCTION

New veterinary medicinal products developed as performance enhancers will have to satisfy all the usual requirements of approval for marketing authorisation, plus certain requirements concerning efficacy and target animal safety, due to their special nature. Therefore, within the framework of clinical efficacy testing, which always includes testing of target animal safety, special attention must be paid to the latter.

This note for guidance is not intended to replace the note for guidance: *Good Clinical Practice for the Conduct of Clinical Trials on Veterinary Medicinal Products in the European Union*, but is intended to provide specific guidance in relation to the documentation of the efficacy of performance enhancers, and should be applied in conjunction with Directive 81/852/EEC and the note for guidance on clinical trials.

For the purpose of this note for guidance, the following definition shall apply:

Performance enhancer: a veterinary medicinal product applied to a healthy animal in order to influence favourably the yield and/or quality of animal produce and/or nutritional efficiency and/or the growth of the animal.

This note for guidance does not cover performance enhancers which are intended to be administered in the form of feed additives.

2. STUDIES CONCERNING THE EFFECTS OF PERFORMANCE ENHANCERS ON TARGET ANIMAL PRODUCE AND TARGET ANIMAL HEALTH

(Assessment of Efficacy and Safety)

2.1 Experimental conditions

The studies which are commonly conducted as field trials should be performed in groups of each target species in comparison with negative control groups.

If applicable, trials should involve a representative cross-section of breeds of the species for which the product is intended, to gain data on possible different responses in different purpose breeds (e.g. inter-breed trials on mono and dual purpose breeds).

Furthermore, different geographic and climatic regions and a wide variety of feeding and rearing conditions in accordance with standard practice in the European Union should be covered (e.g. concentrate/roughage and open pasture feeding).

Where the performance enhancer is intended to improve growth or feed efficiency, animals must be in a marketable condition when final measurements are made.

Performance enhancers are to be tested only in animals showing no signs of any health defects.

With performance enhancers intended to be administered to the animals throughout their life or over repeated periods throughout their life, the duration of experiments has to be sufficient to recognise possible effects due to long-term administration.

The observation period should cover a pre-treatment, a treatment and, where appropriate, a post-treatment period of suitable length in view of the recognition of long-term effects.

The tests performed must be described individually, in detail and in accordance with Directive 81/852/EEC and the note for guidance on clinical trials. In addition, the trial protocol should be carefully drawn up with regard to general herd/animal descriptive data as follows:

Herd: size, feeding and rearing conditions, location.

Animal: breed, age, physiological and general health conditions, yield of animal produce, nutritional composition of the individual daily ration in terms of quality and quantity (if possible, concurrent therapy).

The number of herds/animals involved in the trials must permit a statistical analysis.

2.2 Clinical trials

The following studies should establish the efficacy and safety of the performance enhancer in the target species under conditions of use. They should be performed taking into consideration the results of preclinical trials on target animal pharmacology conducted in accordance with the requirements of the note for guidance on clinical trials.

2.2.1 Dose determination studies

The purpose of these studies is to explain the rationale for the selection of the dose or dose range and the dose intervals claimed to be optimally effective for the selected parameters of desired performance enhancement and, possibly, to demonstrate simultaneously the dose/response relationship. The dose or dose range considered as optimally effective is that beyond which any further increase does not improve desired efficacy or, if a further increase does provide improved efficacy, at which the benefit is outweighed by increased risks in terms of animal and/or human safety. The dose determination will be based on a control (untreated) and at least 3 non-zero levels in target animals.

2.2.2 Dose confirmation studies

These studies will be based on the optimally effective dosage regimen selected from the dose determination studies. They should demonstrate the effects of the final product on yield and/or quality of animal produce, nutritional efficiency and growth of the animal.

The studies should also demonstrate the effective range, possible side effects and contra-indications occurring under the proposed conditions of use of the performance enhancer, taking into account relevant physiological conditions (e.g. pregnancy, lactation) and the results of the studies on pharmacology/toxicology. Therefore, the trials should include the examination of appropriate dose levels and dose intervals as well as treatment periods of sufficient length to elucidate such effects.

The trial protocol should be carefully drawn up with regard to the dosage administered, the method and route of administration and, if applicable, the volume injected per injection site and the location of the injection site.

The following data on efficacy as well as data on adverse effects and further negative effects which occurred during the experiment and the times of their appearance must be provided.

It is virtually impossible to generalise about the way in which the performance enhancers exert their effects (improvement of growth, quality of animal produce, efficiency of feed utilisation, egg production, milk production, wool production, etc.). Therefore, the provision of the data given below as examples should be decided on a case-to-case basis, while allowing for the choice of more suitable and/or additional parameters:

a) Yield of animal produce

The yield of animal produce over appropriate and defined periods of time should be monitored and reported (e.g. the yield of milk once a week).

b) Quality of animal produce

Depending on the kind of animal produce (e.g. edible/non-edible produce) it should be examined for organoleptic, nutritional, hygienic and technological qualities. The following examples of data should be given, with the reservation mentioned above:

- composition of animal produce (e.g. percentages of milk components, such as fat, protein, lactose, vitamins, minerals, hormones, counts of microorganism and somatic cells), physical characteristics (e.g. pH, freezing point);
- composition of carcass (e.g. less fat, more meat, percentages of meat protein, fat moisture);
- suitability of animal produce in respect of food processing (e.g. properties of milk important for cheese-making)

c) Nutritional efficiency and growth of animal

Data should be provided on growth rate, live weight gain, feed intake, efficiency of feed utilisation, efficiency of energy and nutrient utilisation for production of the animal produce, body condition, dependency of the increase of animal produce on the adequate nutritional status of the animal.

d) Health of the animal

- Clinical effects on the target tissues or organs (e.g. udder), cases of illness, the route and duration of treatment, should be reported.
- Local and systemic tolerance should be examined carefully when appropriate (e.g. at the site of administration in case of injections, in the digestive system in case of boli, etc.).
- Animals dying during the trial should be examined (gross and, if applicable, histomorphologic examination).

e) Collection of target animal safety data under field conditions

Depending on the mode of action or the physiological effect of the product, it may be relevant, where appropriate and practicable, to take the opportunity offered by the clinical trials to review the target animal safety data and to confirm that animal welfare is not prejudiced under field conditions. Therefore, some of the following parameters may have to be monitored:

- Metabolic and hormonal functions (e.g. blood hormone tests, pituitary function tests, effects on the pancreas including insulin secretion, metabolic function of the liver, glucose tolerance, fat metabolism and energy balance);
- Extensive observation of behaviour, respiratory, digestive and cardiovascular functions;

– Reproduction performance and fertility (e.g. oestrus cycle, services per conception, conception rate, abortions, birth interval);

– Local irritancy, e.g. at the injection site (macroscopic and histological inspection);

– In order to examine the health of the progeny the following parameters may be evaluated where relevant and practical: birth weight, sex ratio, size and general health at birth; growth characteristics; development and subsequent reproduction performance and fertility.

3. ANALYSIS OF THE RESULTS AND CONCLUSIONS

The report should include all animals involved in the trials. Cases which cannot be assessed due to a lack or loss of data should be reported and their distribution within the groups of animals classified.

The methods of statistical evaluation used should be mentioned and their choice justified.

From the point of view of efficacy and target animal safety, the administration of performance enhancers to healthy animals is justified only when the benefit of use of the product outweighs the risk to animal welfare and when the quality of animal produce is not adversely affected. Therefore, data should be reported in such a way that a careful assessment of the benefit/risk ratio is possible.