ANNEX II

REQUIREMENTS REFERRED TO IN POINT (B) OF ARTICLE 8(1)[(1)]

TITLE I

Requirements for veterinary medicinal products other than immunological veterinary medicinal products

PART 4

Pre-clinical and clinical trial

Chapter III

Particulars and documents

The dossier on efficacy shall include all pre-clinical and clinical documentation and/or results of trials, whether favourable or unfavourable to the veterinary medicinal products, in order to enable an objective overall assessment of the risk/benefit balance of the product.

1. **Results of pre-clinical trials**

Wherever possible, particulars shall be given of the results of:

(a) tests demonstrating pharmacological actions;

(b) tests demonstrating the pharmacodynamic mechanisms underlying the therapeutic effect;

(c) tests demonstrating the main pharmacokinetic profile;

(d) tests demonstrating target animal safety;

(e) tests investigating resistance.

Should unexpected results occur during the course of the tests, these should be detailed.

Additionally, the following particulars shall be provided in all pre-clinical studies:

(a) a summary;

(b) a detailed experimental protocol giving a description of the methods, apparatus and materials used, details such as species, age, weight, sex, number, breed or strain of animals, identification of animals, dose, route and schedule of administration;

(c) a statistical analysis of the results, where relevant;

(d) an objective discussion of the results obtained, leading to conclusions on the efficacy and safety of the veterinary medicinal product.

Total or partial omission of any of these data shall be justified.

2. **Results of clinical trials**

All the particulars shall be supplied by each of the investigators on individual record sheets in the case of individual treatment and collective record sheets in the case of collective treatment.

The particulars supplied shall take the following form:

(a) name, address, function and qualifications of investigator in charge;

(b) place and date of treatment; name and address of owner of the animals;

(c) details of the clinical trial protocol giving a description of the methods used, including methods of randomisation and blinding, details such as the route of administration, schedule of administration, the dose, identification of trial animals, species, breeds or strains, age, weight, sex, physiological status;

(d) method of animal management and feeding, stating the composition of the feed and the nature and quantity of any feed additives;

(e) case history (as full as possible), including occurrence and course of any intercurrent diseases;

(f) diagnosis and means used to make it;

(g) clinical signs, if possible according to conventional criteria;

(h) precise identification of the formulation of the veterinary medicinal product used in the clinical trial and the physical and chemical test results for the relevant batch(es);

(i) dosage of the veterinary medicinal product, method, route and frequency of administration and precautions, if any, taken during administration (duration of injection, etc.);

(j) duration of treatment and period of subsequent observation;

(k) all details concerning other veterinary medicinal products which have been administered during the period of examination, either prior to or concurrently with the test product and, in the latter case, details of any interactions observed;

(l) all results of the clinical trials, fully describing the results based on the efficacy criteria and end points specified in the clinical trial protocol and including the results of the statistical analyses, if appropriate;

(m) all particulars of any unintended event, whether harmful or not, and of any measures taken in consequence; the cause-and-effect relationship shall be investigated if possible;

(n) effect on animals' performance if appropriate;

(o) effects on the quality of foodstuffs obtained from treated animals, particularly in the case of veterinary medicinal products intended for use as performance enhancers;

(p) a conclusion on the safety and efficacy in each individual case or, summarised in terms of frequencies or other appropriate variables where specific mass treatment is concerned.

Omission of one or more items (a) to (p) shall be justified.

The marketing authorisation holder shall make all necessary arrangements to ensure that the original documents, which formed the basis of the data supplied, are kept for at least five years after the veterinary medicinal product is no longer authorised.

In respect of each clinical trial, the clinical observations shall be summarised in a synopsis of the trials and the results thereof, indicating in particular:

(a) the number of control and test animals treated either individually or collectively, with a breakdown according to species, breed or strain, age and sex;

(b) the number of animals withdrawn prematurely from the trials and the reasons for such withdrawal;

(c) in the case of control animals, whether they have:
- received no treatment,
- received a placebo, or
- received another veterinary medicinal product authorised in the Community for the same indication for use in the same target animal species, or
- received the same active substance under investigation in a different formulation or by a different route;

(d) the frequency of observed adverse reactions;

(e) observations as to the effect on animal performance, if appropriate;

(f) details concerning test animals which may be at increased risk owing to their age, their mode of rearing or feeding, or the purpose for which they are intended, or animals the physiological or pathological condition of which requires special consideration;

(g) a statistical evaluation of the results.

Finally, the investigator shall draw general conclusions on the efficacy and safety of the veterinary medicinal product under the proposed conditions of use, and in particular any information relating to indications and contraindications, dosage and average duration of treatment and where, appropriate, any interactions observed with other veterinary medicinal products or feed additives as well as any special precautions to be taken during treatment and the clinical symptoms of overdosage, when observed.

In the case of fixed combination products, the investigator shall also draw conclusions concerning the safety and the efficacy of the product when compared with the separate administration of the active substances involved.

(**1**) This Annex will be amended by the Commission in accordance with Articles 146 and 153. All references to Articles or to 'this Directive' in this Annex, unless otherwise specified, are to be understood as references to Directive 2001/82/EC.

Changes to legislation:
There are currently no known outstanding effects for the Regulation (EU) 2019/6 of the European Parliament and of the Council, Chapter III.