

## [<sup>F1</sup>ANNEX I

### CHEMICAL, PHARMACEUTICAL AND ANALYTICAL STANDARDS, SAFETY AND RESIDUE TESTS, PRE-CLINICAL AND CLINICAL TRIALS IN RESPECT OF TESTING OF VETERINARY MEDICINAL PRODUCTS

#### Textual Amendments

- F1** Substituted by [Commission Directive 2009/9/EC of 10 February 2009 amending Directive 2001/82/EC of the European Parliament and of the Council on the Community code relating to medicinal products for veterinary use \(Text with EEA relevance\)](#).

## TITLE III

### REQUIREMENTS FOR SPECIFIC MARKETING AUTHORISATION APPLICATIONS

#### 1. Generic veterinary medicinal products

Applications based on Article 13 (generic veterinary medicinal products) shall contain the data referred to in Parts 1 and 2 of Title I of this Annex together with an environmental risk assessment and data demonstrating that the product has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product and data showing bio-equivalence with the reference medicinal product. If the reference veterinary medicinal product is a biological medicinal product, the documentation requirements in Section 2 for similar biological veterinary medicinal products shall be fulfilled.

For generic veterinary medicinal products the detailed and critical summaries on safety and efficacy shall particularly focus on the following elements:

- the grounds for claiming essential similarity,
- a summary of impurities present in batches of the active substance(s) as well as those of the finished medicinal product (and where relevant decomposition products arising during storage) as proposed for use in the product to be marketed together with an evaluation of these impurities,
- an evaluation of the bio-equivalence studies or a justification as to why studies were not performed with reference to established guidance,
- if applicable, additional data in order to demonstrate the equivalence of safety and efficacy properties of different salts, esters or derivatives of an authorised active substance shall be provided by the applicant; those data shall include evidence that there is no change in the pharmacokinetic or pharmacodynamic properties of the therapeutic moiety and/or in toxicity, which could influence the safety/efficacy profile.

Every claim in the summary of product characteristics not known from or inferred from the properties of the medicinal product and/or its therapeutic group should be discussed in the non-clinical/clinical overviews/summaries and substantiated by published literature and/or additional studies.

For generic veterinary medicinal products intended to be administered by intramuscular, subcutaneous or transdermal routes, the following additional data shall be provided:

- evidence to demonstrate equivalent or differing depletion of residues from the administration site, which may be substantiated by appropriate residue depletion studies,

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- evidence to demonstrate target animal tolerance at the administration site, which may be substantiated by appropriate target animal tolerance studies.

## 2. Similar biological veterinary medicinal products

In accordance with Article 13(4), where a biological veterinary medicinal product which is similar to a reference biological veterinary medicinal product does not meet the conditions in the definition of generic medicinal product, information to be supplied shall not be limited to Parts 1 and 2 (pharmaceutical, chemical and biological data), supplemented with bio-equivalence and bioavailability data. In such cases, additional data shall be provided, in particular on the safety and efficacy of the product.

- The type and amount of additional data (i.e. toxicological and other safety studies and appropriate clinical studies) shall be determined on a case-by-case basis in accordance with relevant scientific guidelines.
- Due to the diversity of biological veterinary medicinal products, the competent authority shall determine the necessary studies foreseen in Parts 3 and 4, taking into account the specific characteristic of each individual biological veterinary medicinal product.

The general principles to be applied shall be addressed in guideline which shall be adopted by the Agency, taking into account the characteristics of the concerned biological veterinary medicinal product. If the reference biological veterinary medicinal product has more than one indication, the efficacy and safety of the biological veterinary medicinal product claimed to be similar shall be justified or, if necessary, demonstrated separately for each of the claimed indications.

## 3. Well-established veterinary use

For veterinary medicinal products the active substance(s) of which has/have been in ‘well-established veterinary use’ as referred to in Article 13a, with recognised efficacy and an acceptable level of safety, the following specific rules shall apply.

The applicant shall submit Parts 1 and 2 as described in Title I of this Annex.

For Parts 3 and 4, a detailed scientific bibliography shall address all aspects of the safety and efficacy.

The following specific rules shall apply in order to demonstrate the well-established veterinary use:

- 3.1. The following factors shall be taken into account in order to establish a well-established veterinary medicinal use of constituents of veterinary medicinal products:
  - (a) the time over which an active substance has been used;
  - (b) quantitative aspects of the use of the active substance;
  - (c) the degree of scientific interest in the use of the active substance (reflected in the published scientific literature);
  - (d) the coherence of scientific assessments.

Different periods of time may be necessary for establishing well-established use of different substances. In any case, however, the period of time required for establishing a well-established veterinary use of a constituent of a medicinal product shall not be less than ten years from the first systematic and documented use of that substance as a veterinary medicinal product in the Community.

- 3.2. The documentation submitted by the applicant shall cover all aspects of the safety and/or efficacy assessment of the product for the proposed indication in the target species using the proposed route of administration and dosage regimen. It must include or refer to a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies. All documentation, both favourable and unfavourable, shall be communicated. With respect to the provisions on well-established veterinary use, it is in particular necessary to clarify that bibliographic reference to other sources of evidence (post-marketing studies, epidemiological studies etc.) and not just data related to tests and trials may serve as a valid proof of safety and efficacy of a product if an application explains and justifies the use of these sources of information satisfactorily.
  - 3.3. Particular attention must be paid to any missing information and justification must be given as to why demonstration of an acceptable level of safety and/or efficacy can be supported although some studies are lacking.
  - 3.4. The detailed and critical summaries regarding safety and efficacy must explain the relevance of any data submitted which concern a product different from the product intended for marketing. A judgement must be made whether or not the product studied can be considered as similar to the product, for which application for a marketing authorisation has been made in spite of the existing differences.
  - 3.5. Post-marketing experience with other products containing the same constituents is of particular importance and applicants shall put a special emphasis on this issue.
4. Combination veterinary medicinal products

For applications based on Article 13b, a dossier containing Parts 1, 2, 3 and 4 shall be provided for the combination veterinary medicinal product. It shall not be necessary to provide studies on the safety and efficacy of each active substance. It shall nevertheless be possible to include information on the individual substances in the application for a fixed combination. The submission of data on each individual active substance, in conjunction with the required user safety studies, residues depletion studies and clinical studies on the fixed combination product, may be considered a suitable justification for omitting data on the combination product, based on animal welfare grounds and unnecessary testing on animals, unless there is suspected interaction leading to added toxicity. Where applicable, information regarding the manufacturing sites and the safety evaluation of adventitious agents shall be provided.

5. Informed consent applications

Applications based on Article 13c shall contain the data described in Part 1 of Title 1 of this Annex, provided that the marketing authorisation holder for the original veterinary medicinal product has given the applicant his consent to refer to the content of Parts 2, 3 and 4 of the dossier of that product. In this case, there is no need to submit quality, safety and efficacy detailed and critical summaries.

6. Documentation for applications in exceptional circumstances

A marketing authorisation may be granted subject to certain specific obligations requiring the applicant to introduce specific procedures, in particular concerning the safety and efficacy of the veterinary medicinal product, when, as provided for in Article 26(3) of this Directive, the applicant can show that he is unable to provide comprehensive data on the efficacy and safety under normal conditions of use.

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The identification of essential requirements for all applications mentioned in this section should be subject to guidelines which shall be adopted by the Agency.

#### 7. Mixed marketing authorisation applications

Mixed marketing authorisation applications are applications where Part(s) 3 and/or 4 of the dossier consist of safety and efficacy studies carried out by the applicant as well as bibliographical references. All other part(s) are in accordance with the structure described in Part I of Title I of this Annex. The competent authority shall accept the proposed format presented by the applicant on a case-by-case basis.]