EUROPEAN
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ANNEX 1

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APPLICATION / REQUEST FOR THE ESTABLISHMENT OF MAXIMUM RESIDUE LIMITS

1. The application or the request shall include all administrative information and scientific documentation necessary for demonstrating the safety of the residues of the substance in question and risk management considerations.
2. All volumes of the dossier shall be clearly numbered and paginated. Particular care shall be taken to ensure that there is adequate cross-referencing between volumes and between the detailed and critical summaries and the original data. Electronic submissions shall comply with guidance on veterinary e-Submissions published by the EMA.
3. Where reference is made to published information, complete copies of the relevant articles should be inserted in the relevant section of the dossier.
4. The application or the request shall be submitted in accordance with the requirements specified below respecting the order of presentation indicated.
5. Pharmacological, toxicological and residue tests, results of which are accompanying an application or a request for the establishment of MRLs, shall be carried out in conformity with Directive 2004/10/EC of the European Parliament and of the Council[1] and Directive 2010/63/EU of the European Parliament and of the Council[2].

Chapter 1 Administrative information

The administrative information shall comprise two parts, one providing the administrative data and the second providing a summary of the evaluation proposed by the applicant/requestor.

The following details shall be included:

Part 1 – Administrative data:

- name of the substance for review, using international non-proprietary name (INN) where attributed;
- name and address of the applicant/requestor;
- name and address details of the applicant/requestor contact point for all correspondence related to the application;

Part 2 – Summary of the evaluation proposed by the applicant/requestor:

- name of the substance for review, using INN where attributed;

[1] Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances, (OJ L 50, 20.2.2004, p. 44).

[2] Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes (OJ L 276, 20.10.2010, p. 33).

- clarification on whether the substance is used in the product as active ingredient, excipient, preservative, etc.;

- summary of anticipated pattern of veterinary use (target species, major indications, dose-regimen);

- information on any applications to other Union or international bodies, the dates of these applications and the outcome;

- summary of the findings:

- relevant no-observed (adverse) effect levels (NO(A)EL) or an accepted alternative for the safety evaluation,
- reference to relevant study,
- uncertainty factor proposed,
- Acceptable Daily Intake (ADI) proposed, or an alternative in accordance with Article 6 of Regulation (EC) No 470/2009,
- marker residue (where relevant),
- MRLs proposed (where relevant),
- method of analysis proposed (including limit of quantification and reference, where relevant).

Chapter 2 Data for scientific risk assessment

A. Safety file

The dossier of safety tests shall include the following documents:

– an index of all studies included in the dossier,

– a statement confirming that all data known to the applicant/requestor at the time of submission, whether favourable or unfavourable, are included,

– a justification for the omission of any type of study,

– an explanation for the inclusion of an alternative type of study,

– in cases where a study pre-dates Directive 2004/10/EC or Good Laboratory Practice status is unknown, a discussion of the contribution that any non-GLP study can make to the overall risk assessment.

Each study report shall include the following documents:

– a copy of the study plan (protocol, including amendments and deviations),

– a signed statement of compliance with good laboratory practice, where applicable,

– a description of the methods, apparatus and materials used,

– a description and justification of the test system,

– a description of the results obtained, in sufficient detail to allow the results to be critically evaluated independently of their interpretation by the author,

– a statistical analysis of the results where appropriate,

– a discussion of the results, with comment on observed (adverse) effect levels and NO(A)ELs, and on any unusual findings,

– a detailed description and a thorough discussion of the results of the study.

A.0. Detailed and critical summary

The detailed and critical summary shall be signed and dated. Information about the author's educational background, training and occupational experience shall be attached. The professional relationship of the author with the applicant/requestor shall be declared.

All the important data shall be summarised in an Annex, in tabular or graphic form whenever possible and the relevant bibliographic references shall also be included in the Annexes to the document. The relevance of the studies provided for the evaluation of potential risks presented by residues to humans shall be addressed. The detailed and critical summary and its Annexes shall contain precise cross-references to the information contained in the main documentation. This section shall not introduce new studies that are not included in the main documentation.

A.1. Precise identification of the substance concerned by the application/ request:

A.1.1 INN,

A.1.2 International Union of Pure and Applied Chemistry (IUPAC) name,

A.1.3 Chemical Abstract Service (CAS) number,

A.1.4 therapeutic, pharmacological and chemical classification,

A.1.5 synonyms and abbreviations,

A.1.6 structural formula,

A.1.7 molecular formula,

A.1.8 molecular weight,

A.1.9 degree of impurity,

A.1.10 qualitative and quantitative composition of impurities,

A.1.11 description of physical properties,

A.1.11.1 melting point,

A.1.11.2 boiling point,

A.1.11.3 vapour pressure,

A.1.11.4 solubility in water and organic solvents expressed in g/l, with indication of temperature,

A.1.11.5 density,

A.1.11.6 spectra of refraction, rotation, etc.,

A.1.11.7 pKa,

A.1.11.8 protein binding.

A.2. pharmacology;

A.2.1 pharmacodynamics;

A.2.2 pharmacokinetics in laboratory species (absorption, distribution, metabolism, excretion);

A.3. toxicology (in laboratory species);

A.3.1 single-dose toxicity, where available;

A.3.2 repeat-dose toxicity;

A.3.2.1 repeat-dose (90-day) oral toxicity testing;

A.3.2.2 repeat-dose (chronic) toxicity testing;

A.3.3 tolerance in target species, where available;

A.3.3 reproductive toxicity, including developmental toxicity;

A.3.3.1 study of the effects on reproduction;

A.3.3.2 study of developmental toxicity;

A.3.4 genotoxicity;

A.3.5 carcinogenicity;

A.4. other requirements;

A.4.1 special studies (e.g. immunotoxicity, neurotoxicity);

A.4.2 microbiological properties of residues (if relevant);

A.4.2.1 potential effects on the human gut flora;

A.4.2.2 potential effects on the microorganisms used for industrial food processing;

A.4.3 observations in humans;

A.5 determination of ADI or alternative limit.

B. Residue File

The dossier of residue tests shall include the following documents:

– an index of all studies included in the dossier;

– a statement confirming that all data known to the applicant/requestor at the time of submission, whether favourable or unfavourable, are included;

– a justification for the omission of any type of study;

– an explanation for the inclusion of an alternative type of study;

– in cases where a study pre-dates Directive 2004/10/EC or GLP status is unknown, a discussion of the contribution that any non-GLP study can make to the overall risk assessment.

Each study report shall include the following documents:

– a copy of the study plan (protocol, including amendments and deviations);

– a signed statement of compliance with GLP, where applicable;

– a description of the methods, apparatus and materials used;

– a description and justification of the test system;

– a description of the results obtained, in sufficient detail to allow the results to be critically evaluated independently of their interpretation by the author;

– a statistical analysis of the results where appropriate;

– a discussion of the results;

– a detailed description and a thorough discussion of the results of the study.

B.0. Detailed and critical summary

The detailed and critical summary shall be signed and dated. Information about the author's educational background, training and occupational experience shall be attached. The professional relationship of the author with the applicant/requestor shall be declared.

All the important data shall be summarised in an Annex, in tabular or graphic form whenever possible and the relevant bibliographic references shall also be included in the Annexes to the document. The relevance for the studies provided for the establishment of maximum residue limits shall be discussed. The detailed and critical summary and the Annexes shall contain precise cross-references to the information contained in the main documentation. That section shall not introduce new studies that are not included in the main documentation.

B.1. Metabolism and residue kinetics:

B.1.1 pharmacokinetics in food producing species (absorption, distribution, metabolism, excretion);

B.1.2. depletion of residues:

B.1.2.1 identification of marker residue;

B.1.2.2 ratio of marker to total residues;

B.2. monitoring and exposure data, if relevant;

B.3. residue analytical method;

B.3.1 description of the method, according to an internationally agreed format;

B.3.2 validation of the method in accordance with relevant guidance published by the Commission and the EMA.

Chapter 3 Risk management considerations

Based on the risk assessment performed, relevant risk management recommendations in accordance with Article 7 of Regulation (EC) No 470/2009 shall be addressed, in particular:

– other legitimate factors such as technological aspects of food and feed productions, feasibility of controls, conditions of use and application of the substances in veterinary medicinal products;

– other relevant risk management considerations for the establishment of MRLs;

– elaboration of MRLs;

– considerations on possible extrapolation of MRLs.