EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

PUBLIC CONSULTATION PAPER

IMPLEMENTATION OF THE NEW REGULATION ON MAXIMUM RESIDUE LIMITS

CONTRIBUTION FOR A FUTURE COMMISSION REGULATION ON FORMAT AND CONTENT OF APPLICATIONS AND REQUESTS SUBMITTED FOR AN OPINION ON A MAXIMUM RESIDUE LIMIT FOR A PHARMACOLOGICALLY ACTIVE SUBSTANCE

Deadline for Public Consultation: 6 July 2009

This document does not represent an official position of the European Commission. It is a tool to explore the views of interested parties on a preliminary proposal. The suggestions contained in this document do not prejudge the form and content of any future proposal by the European Commission.

This document is to be read together with the Commission proposal for a regulation of the European Parliament and of the Council laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin, and repealing Regulation (EEC) No 2377/90 (COM(2007) 194 final) of 17 April 2007 and the Council's Common Position of 18 December 2008 (15079/2/08 REV 2) as voted in the European Parliament on 2 April 2009.

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1. ABOUT THE CONSULTATION

1.1. What is the purpose of this consultation?

On 17 April 2007 the European Commission adopted a proposal for a regulation of the European Parliament and of the Council laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin, and repealing Regulation (EEC) No 2377/90 (COM(2007) 194 final)[1]. This regulation has not been formally adopted yet, but on 2 April 2009 the European Parliament has voted in second reading endorsing the Council's Common position[2]. The entry into force of the new regulation is scheduled for the end of May/beginning of June 2009. The new regulation establishes in its Article 13(1) that the Commission shall, in consultation with the European Medicines Agency (EMEA), adopt measures regarding the form and content of the applications and requests referred to in Articles 3 and 9.

On the basis of the above said, the European Commission intends to draft a Commission Regulation regarding the format and content of the applications and requests referred to in Articles 3 and 9 of the new regulation.

In preparation of this, the EMEA was asked for a contribution concerning the requirements as regards the format and content for an application or a request for an opinion on a maximum residue limit.

With this public consultation, the Directorate General for Enterprise and Industry intends to consult all stakeholders on the contribution of the EMEA.

With this public consultation, the Directorate General for Enterprise and Industry is committed to ensure that all stakeholders can make their views known on this important issue.

This document does not represent an official position of the European Commission. Based on this contribution and on the results of the public consultation, the Directorate General for Enterprise and Industry will prepare a regulation for adoption by the Commission through comitology (regulatory procedure). Requirements on format and content for an application or a request for an opinion on a maximum residue limit shall be annexed to this regulation.

1.2. Who is consulted?

Contributions are invited from all stakeholders dealing with medicines for veterinary use. Stakeholders who are not established within the European Union are equally invited to comment.

1.3. How can I contribute?

Contributions should be sent by e-mail to Jan-Henrik.ROTHERT@ec.europa.eu **before 6 July 2009**. An acknowledgement of receipt will be issued for each contribution received, within five working days. Contributions will be made publicly available on the 'Pharmaceuticals' website of the Commission once the consultation period is over, unless a

[1] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2007:0194:FIN:EN:PDF
[2] http://register.consilium.europa.eu/pdf/en/08/st15/st15079-re02.en08.pdf

specific request for confidentiality is made, in which case only an indication of the contributor will be disclosed. If you do not wish your contribution to be made public, please clearly indicate so.

1.4. What will happen next?

All contributions will be carefully analysed. A summary of the outcome of the consultation will be published on the 'Pharmaceuticals' website of the European Commission and also sent directly to all contributors. The future regulation on the format and the content of applications and requests submitted for an opinion for a maximum residue limit for a pharmacologically active substance will build on this consultation.

1.5. Any questions?

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2. THE CONTRIBUTION ON FORMAT AND CONTENT OF APPLICATIONS AND REQUESTS SUBMITTED FOR AN OPINION ON A MAXIMUM RESIDUE LIMIT ON A PHARMACOLOGICALLY ACTIVE SUBSTANCE

2.1. Background

The use of veterinary medicinal products in food-producing animals may result in the presence of residues in foodstuffs obtained from treated animals. The same applies where biocidal products containing pharmacologically active substances are used in animal husbandry.

Currently pharmacologically active substances are classified in four annexes to Council Regulation (EEC) No 2377/90 of 26 June 1009 laying down a Community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin according to whether a maximum residue limit is established, a maximum residue limit is not necessary to be established, a provisional maximum residue limit is established or a maximum residue limit cannot be established because residues of a given substance, at whatever limit, constitute a hazard to human health.

Applications for an opinion for a maximum residue limit have to be submitted in accordance with Annex V to Council Regulation (EEC) No 2377/90.

In order to address various shortcomings of the current system, the European Commission adopted on 17 April 2007 a proposal for a regulation of the European Parliament and of the Council laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin, and repealing Regulation (EEC) No 2377/90 (COM(2007) 194 final).

This regulation has not been formally adopted yet, but on 2 April 2009 the European Parliament has voted in second reading endorsing the Council's Common position. The entry into force of the new regulation is scheduled for the end of May/beginning of June 2009.

Article 13(1) of the new regulation as it has been voted by the European Parliament on 2 April 2009 foresees that the Commission shall, in consultation with the Agency, adopt measures regarding the form and content of the applications and requests referred to in Articles 3 and 9 of the new regulation.

On this basis the European Commission intends to adopt as an implementing measure a Commission regulation in relation to the form and the content for an opinion for a maximum residue limit in order to replace Annex V of Council Regulation (EEC) No 2377/90 after it has been repealed. Requirements on format and content of an application or a request shall be annexed to this future regulation.

Following Article 13(1) of the new regulation, the Agency has been consulted and has been asked for a contribution on the requirements in relation to the format and the content. This consultation is based on the contribution submitted by the Agency. It has been produced by the Agency in collaboration with the Committee on Veterinary Medicinal Products ('CVMP') and is annexed to this Consultation paper.

2.2. Scope

Article 13(1) of the new regulation establishes that the Commission shall, in consultation with the Agency, adopt measures regarding the format and content of the applications and requests referred to in Articles 3 and 9. Requirements as regards the format and the content for all sorts of applications and requests foreseen in the new regulation shall be included in one document which shall be annexed to a future regulation.

These requirements apply to:

- **Applications** for an opinion of the Agency on the maximum residue limit on a pharmacologically active substance intended for use in the Community in veterinary medicinal products which are to be administered to food-producing animals which have to be submitted by:

  ► the **applicant for a marketing authorisation** for a veterinary medicinal product in which such a substance is used,

  ► a **person intending to apply** for such a marketing authorisation or, where appropriate,

  ► the **holder of** such **a marketing authorisation**.

- **Requests** for an opinion on maximum residue limits to the Agency which may be submitted by:

  ► the **European Commission** or a **Member State** where a pharmacologically active substance is authorised for use in a **veterinary medicinal product in a third country** and no application for the establishment of a maximum residue limit for that substance in respect of the foodstuff or species concerned has been submitted pursuant to Article 3 or where a pharmacologically active substance is included in a **medicinal product intended to be used pursuant to Article 11 of Directive 2001/82/EC** and no application for the establishment of a maximum residue limit for that substance in respect of the foodstuff or species concerned has been submitted pursuant to Article 3.

► an **interested party or organisation** in cases where a pharmacologically active substance is included in a medicinal product intended to be used pursuant to Article 11 of Directive 2001/82/EC and no application for the establishment of a maximum residue limit for that substance in respect of the foodstuff or species concerned has been submitted pursuant to Article 3 and **minor species or minor uses** are concerned.

The requests foreseen under this bullet point constitute novelties insofar as, in particular third parties, Member States and the European Commission may now submit requests for an opinion for a maximum residue limit under specific conditions.

- **Applications** submitted for a pharmacologically active substance contained in a **biocidal product used in animal husbandry**.

  Pharmacologically active substances contained in a biocidal product used in animal husbandry might equally lead to residues in foodstuffs of animal origin. The new regulation includes these substances in order to ensure that they are scientifically assessed following the same procedure as pharmacologically active substances contained in veterinary medicinal products.

- The **Accelerated procedure**: The European Commission, any person having submitted an application under Article 3, or a Member State may ask the Agency to carry out an accelerated procedure for the assessment of the maximum residue limit of a pharmacologically active substance contained in veterinary medicinal products or biocidal products used in animal husbandry where a given product needs to be authorised as a matter of urgency.

  An accelerated procedure has been introduced into the new regulation allowing addressing situations of urgency.

- The **Review of an opinion**: The European Commission, an applicant under Article 3 of the new regulation or a Member State may request the Agency to issue a new opinion on a maximum residue limit where they consider it necessary in order to protect human or animal health as a result of new information.

- **Extensions of an existing maximum residue limit** for a given pharmacologically active substance to other foodstuffs or species.

2.3. Structure

The contribution in Annex is structured in two sections:

- An introduction and general principles as regards the format and the content for an application and a request for an opinion on maximum residue limit.

- A detailed description of the dossier requirements.

We invite stakeholders to comment on all aspects and in particular on the new elements of the new regulation.

3. ANNEX

European Medicines Agency
Veterinary Medicines and Inspections

EMEA/CVMP/126767/2009
London, 29April 2009

FORMAT AND CONTENT OF APPLICATIONS FOR THE ESTABLISHMENT OF MAXIMUM RESIDUE LIMITS

INTRODUCTION AND GENERAL PRINCIPLES

1 The particulars and documents accompanying an application for the establishment of maximum residue limits pursuant to Articles 3, 9 and 15 and Regulation (EC) No xxxx 2009 shall be presented in accordance with the requirements set out in this Annex and shall take into account the guidance published by the Commission in *The rules governing medicinal products in the European Union*, Volume 8, Notice to applicants and guidelineVeterinary medicinal products, Establishment of maximum residue limits (MRLs) for residues of veterinary medicinal products in foodstuffs of animal origin.

2 In assembling the dossier for application for the establishment of maximum residue limits, applicants shall also take into account the current state of scientific knowledge and the scientific guidance relating to the safety of residues published by the European Medicines Agency (Agency).

3 All information which is relevant to the evaluation of the safety of residues of the substance concerned shall be included in the application, whether favourable or unfavourable to the substance. In particular, all relevant details shall be given of any incomplete or abandoned test or trial relating to the substance.

4 Pharmacological, toxicological, residue and safety tests shall be carried out in conformity with the provisions related to Good Laboratory Practice (GLP) laid down in Directive 2004/10/EC of the European Parliament and of the Council and Directive 2004/9/EC of the European Parliament and of the Council.

5 Member States shall ensure that all experiments on animals are conducted in accordance with Council Directive 86/609/EEC

6 Where the extension of existing maximum residue limits to other animal species or specific food commodities is requested, normally only a dossier consisting of an application form and a residue file should be submitted. Safety data may be required in cases where the risk assessment performed with regard to the previous application would not be applicable to the extension proposed.

7 The dossier shall comprise:

- Administrative information;
- Data for risk assessment;
  - Safety file, including the detailed and critical summaries on the results of the safety studies
  - Residue file, including the detailed and critical summaries on the results of the residue studies
- Risk management considerations

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8 All volumes should be clearly numbered and paginated. Particular care should be taken to ensure that there is adequate cross-referencing between volumes and between the detailed and critical summaries and the original data.

Where reference is made to published information, complete copies of the relevant articles should be inserted at the relevant point of the dossier.

CONTENT OF THE DOSSIER

The application 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, where appropriate. The application shall be submitted in accordance with the requirements specified below respecting the order of presentation indicated.

Chapter 1 Administrative information

The administrative application should comprise two parts, one providing the administrative data and the second providing a summary of the evaluation proposed by the applicant.

The following details should be included:

Part 1 – Administrative data

Name of the substance for review (Using INN where attributed);
Name and address of the applicant;
Summary of anticipated pattern of veterinary use (target species, major indications, dose-regimen);
Clarification on whether the substance is used in the product as active ingredient, excipient, preservative, etc;
Name, address, telephone number, fax number and e-mail address of the company contact point for all correspondence related to the application;

Part 2 – Summary of the evaluation proposed by the applicant

Name of the substance for review;
Relevant NO(A)EL or an accepted alternative for the safety evaluation;
Reference to relevant study;
Uncertainty factor proposed;
ADI proposed, or an alternative in accordance with Article 6 of Regulation xxx/2009;
MRLs proposed (if relevant);
Method of analysis proposed (including limit of quantification and reference);
Information concerning scientific evaluations by EU or international bodies.

Chapter 2 Data for scientific risk assessment

A. Safety file

The dossier of safety tests shall include:

- an index of all studies included in the dossier;
- a statement confirming that all data known to the applicant at the time of submission, whether favourable or unfavourable, are included;
- a justification for the omission of any type of study;
- an explanation of the inclusion of an alternative type of study;

- a discussion of the contribution that any study that pre-dates studies performed in line with good laboratory practice (GLP) according to Directive 2004/10/EC can make to the overall risk assessment.

Each study report shall include:

- a copy of the study plan (protocol),
- a 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 and NO(A)ELs, and on any unusual findings,
- a detailed description and a thorough discussion of the results of the study and their relevance for the evaluation of potential risks presented by residues to humans.

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 shall be declared.

All important data shall be summarised in an annex, whenever possible in tabular or graphic form and the relevant bibliographic references should also be included in annexes to document. The detailed and critical summary and its annexes shall contain precise cross-references to the information contained in the main documentation.

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

- International non-proprietary name (INN);
- International Union of Pure and Applied Chemistry (IUPAC) name;
- Chemical Abstract Service (CAS) number;
- Therapeutic, pharmacological and chemical classification;
- Synonyms and abbreviations;
- Structural formula;
- Molecular formula;
- Molecular weight;
- Degree of impurity;
- Qualitative and quantitative composition of impurities;

- Description of physical properties:
  - Melting point
  - Boiling point
  - Vapour pressure
  - Solubility in water and organic solvents expressed in g/l, with indication of temperature
  - Density
  - Spectra of refraction, rotation etc.

A.2. Pharmacology

A.2.1 Pharmacodynamics

A.2.2 Pharmacokinetics

A.3. Toxicology

A.3.1 Single-dose toxicity, where appropriate

A.3.2 Repeat-dose toxicity

A.3.2.1 *Repeat-dose (90-day) oral toxicity testing*

A.3.2.2 *Repeated dose (chronic) toxicity testing*

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

A.4.2.1 *Disruption of the colonisation barrier*

A.4.2.2 *Increase of the population of resistant bacteria*

A.4.3 Observations in humans

A.5 Determination of ADI or alternative limit

B. Residue File

The dossier of residue tests shall include:

- an index of all studies included in the dossier;
- a statement confirming that all data known to the applicant at the time of submission, whether favourable or unfavourable, are included;
- a justification for the omission of any type of study;
- an explanation of the inclusion of an alternative type of study;
- a discussion of the contribution that any study that pre-dates studies performed in line with good laboratory practice (GLP) according to Directive 2004/10/EC can make to the overall risk assessment.

Each study report shall include:

- a copy of the study plan (protocol);
- a 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;
- a detailed description and a thorough discussion of the results of the study and their relevance for the establishment of maximum residue limits.

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 shall be declared.

All important data shall be summarised in an annex, whenever possible in tabular or graphic form and the relevant bibliographic references should also be included in annexes to the document. The detailed and critical summary and the annexes shall contain precise cross-references to the information contained in the main documentation.

B.1. Metabolism and residue kinetics

B.1.1 Pharmacokinetics (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

B.2.1 For substances used in veterinary medicinal products monitoring or exposure data, if relevant

B.2.2 For substances used in biocidal products, relevant information in order to establish the exposure and residue concentrations through use of a biocide

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:

- Specificity;
- Accuracy;
- Precision;
- Limit of detection;
- Limit of quantification;
- Practicability and applicability under normal laboratory conditions;
- Susceptibility to interference;
- Stability of incurred residues.

Chapter 3 Risk management considerations

Based on the risk assessment performed, relevant risk management recommendations in accordance with Article 7 of Regulation xxxx/2009 should be addressed, in particular:

1. Potential effects on the microorganisms used for industrial food processing, if relevant;
2. Other relevant risk management considerations for the establishment of maximum residue limits;
3. Proposal for the establishment of maximum residue limits;
4. Consideration on possible extrapolation of MRLs.