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Commission Regulation (EC) No 429/2008 of 25 April 2008 on detailed rules for the implementation of Regulation (EC) No 1831/2003 of the European Parliament and of the Council as regards the preparation and the presentation of applications and the assessment and the authorisation of feed additives (Text with EEA relevance)

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Commission Regulation (EC) No 429/2008

of 25 April 2008

on detailed rules for the implementation of Regulation (EC) No 1831/2003 of the European Parliament and of the Council as regards the preparation and the presentation of applications and the assessment and the authorisation of feed additives

(Text with EEA relevance)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition [1], and in particular Article 7(4) and (5) thereof,

After consulting the European Food Safety Authority in accordance with Article 7(4) and (5) of Regulation (EC) No 1831/2003,

Whereas:

(1) It is necessary to establish implementing rules concerning the procedure for the authorisation of feed additives under Regulation (EC) No 1831/2003, including rules for the preparation and the presentation of the applications and for the assessment and the authorisation of such additives. These rules are intended to replace the provisions laid down in the Annex to Council Directive 87/153/EEC [2] fixing guidelines for the assessment of additives in animal nutrition.

(2) Those rules should provide for the requirements to be satisfied by the dossier accompanying the application. They should, in particular, set out the scientific data to be submitted for the identification and the characterisation of the additive concerned and the studies to be submitted to demonstrate its efficacy and its safety for humans, animals and the environment in view of the verification and assessment of the applications for authorisation by the European Food Safety Authority (the Authority).

(3) Depending on the nature of the additive or its requested conditions of use, the extent of the studies necessary to evaluate its properties or its effects may vary. Operators should, therefore, be granted some flexibility with respect to the kind of studies and material to be submitted to demonstrate the safety and the efficacy of the additive concerned. Operators making use of that flexibility should have to justify their choice in the dossier.

(4) The Authority should have the possibility to request supplementary information, where appropriate, in order to determine whether the additive complies with the conditions for authorisation referred to in Article 5 of Regulation (EC) No 1831/2003.

(5) It is indispensable to apply appropriate quality standards when developing dossiers for additives intended for use in feed or water to ensure that the results of laboratory tests are not disputed.

(6) Where necessary, specific requirements should be established for each category of additives referred to in Article 6(1) of Regulation (EC) No 1831/2003.

(7) To stimulate efforts to obtain authorisations for minor species while keeping the necessary level of safety, specific conditions should be provided for taking into account the possibility of extrapolating the results of the studies carried out on major species to minor species.

(8) Implementing rules concerning applications for authorisation should take into account different requirements for food-producing animals and other animals, for which aspects regarding the safety evaluation for the human consumer are not relevant.

(9) Recourse to procedures involving the use of laboratory animals for experimental or other scientific purposes and animal testing according to Council Directive 86/609/EEC of 24 November 1986 on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of the animals used for experimental and other scientific purposes [3] should be kept to a minimum.

(10) To avoid repeating studies unnecessarily, simplified procedures should be provided for the authorisation of additives already authorised for use in food.

(11) As regards additives already authorised without a time limit under Council Directive 70/524/EEC [4], where appropriate, the possibility should be provided for the applicant to demonstrate efficacy, where studies are not available, by any other material which is available to demonstrate efficacy, in particular material concerning the long history of use of the additive concerned.

(12) Rules should be provided for applications for modifications of authorisations in accordance with Article 13(3) of Regulation (EC) No 1831/2003.

(13) Rules should also be provided for applications for the renewal of authorisation under Article 14 of Regulation (EC) No 1831/2003.

(14) With respect to the provisions concerning the safety and efficacy studies to be carried out in support of the application, it is necessary to provide for a transitional period during which the present rules continue to apply. Applications submitted before the entry into force of this Regulation should continue to be treated in accordance with the Annex to Directive 87/153/EEC. With respect to applications submitted during a certain period after entry into force, taking into account the long period of time required for some studies, applicants should have a choice between the rules provided for in this Regulation and the Annex to Directive 87/153/EEC. The implementing rules have been drawn up on the basis of present scientific and technical knowledge and they should be adapted if necessary to any new developments.

(15) The measures provided for in this Regulation are in accordance with the opinion of the Standing Committee on the Food Chain and Animal Health,

HAS ADOPTED THIS REGULATION:

Article 1

Definitions

The following definitions shall apply for the purpose of this Regulation:

1. "pets and other non-food producing animals" means animals belonging to species normally nourished, bred or kept, but not consumed by humans, except horses;

2. "minor species" means food-producing animals other than bovines (dairy and meat animals, including calves), sheep (meat animals), pigs, chickens (including laying hens), turkeys and fish belonging to the Salmonidae.

Article 2

Application

1. An application for the authorisation of a feed additive, as provided for in Article 7 of Regulation (EC) No 1831/2003, shall be submitted using the form set out in Annex I.

It shall be accompanied by a dossier as provided for in Article 3 (hereinafter "the dossier"), containing the particulars and documents referred to in Article 7(3) of Regulation (EC) No 1831/2003.

2. Where, in accordance with Article 18 of Regulation (EC) No 1831/2003, the applicant requests certain parts of the dossier referred to in paragraph 1 to be kept confidential, he shall provide verifiable justification for each document or each part of a document that disclosure of this information might significantly harm its competitive position. Confidential parts shall be submitted separately from the rest of the dossier and shall not be included in the summary referred to in Article 7(3)(h) of Regulation (EC) No 1831/2003. The applicant shall send to the Commission a copy of the parts of the dossier requested to be treated as confidential and of the accompanying justification.

Article 3

Dossier

1. The dossier shall adequately and sufficiently demonstrate that the feed additive satisfies the conditions for authorisation provided for in Article 5 of Regulation (EC) No 1831/2003.

2. The general requirements for the preparation and presentation of the dossier shall be as set out in Annex II.

The specific requirements to be satisfied by the dossier, in the case concerned, shall be as set out in Annex III.

The minimum duration of long term studies shall be as set out in Annex IV.

3. By way of derogation from paragraph 2, the applicant may submit a dossier not satisfying the requirements provided for in paragraph 2, provided that he submits a justification for each element not complying with those requirements.

Article 4

Transitional measures

1. To applications for authorisation submitted before the date of entry into force of this Regulation the Annex to Directive 87/153/EEC shall continue to apply.

2. For applications for authorisation submitted before 11 June 2009 applicants may choose the continued application of Sections III and IV of Parts I and II of the Annex to Directive 87/153/EEC instead of points 1.3, 1.4, 2.1.3, 2.1.4, 2.2.3, 2.2.4, 3.3, 3.4, 4.1.3, 4.1.4, 4.2.3, 4.2.4, 5.3, 5.4, 6.3, 6.4, 7.3, 7.4, 8.3 and 8.4 of Annex III and instead of the provisions laid down in the column "Minimum duration of long term efficacy studies" of the tables of Annex IV.

Article 5

Entry into force

This Regulation shall enter into force on the 20th day following its publication in the Official Journal of the European Union.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels, 25 April 2008.

For the Commission

Androulla Vassiliou

Member of the Commission

[1] OJ L 268, 18.10.2003, p. 29. Regulation as amended by Commission Regulation (EC) No 378/2005 (OJ L 59, 5.3.2005, p. 68).

[2] OJ L 64, 7.3.1987, p. 19. Repealed by Regulation (EC) No 1831/2003.

[3] OJ L 358, 18.12.1986, p. 1. Directive as amended by Directive 2003/65/EC of European Parliament and the Council (OJ L 230, 16.9.2003, p. 32).

[4] OJ L 270, 14.12.1970, p. 1. Directive as last amended by Commission Regulation (EC) No 1800/2004 (OJ L 317, 16.10.2004, p. 37).

ANNEX I

APPLICATION FORM REFERRED TO IN ARTICLE 2(1) AND ADMINISTRATIVE DATA

1. APPLICATION FORM

EUROPEAN COMMISSION

HEALTH AND CONSUMER PROTECTION

DIRECTORATE-GENERAL

(Address)

Date: ….

Subject : Application for authorisation of a feed additive in accordance with Regulation (EC) No 1831/2003.

 Authorisation of a feed additive or a new use of a feed additive (Article 4(1) of Regulation (EC) No 1831/2003)

 Authorisation of an existing product (Article 10(2) or 10(7) of Regulation (EC) No 1831/2003)

 Modification of an existing authorisation (Article 13(3) of Regulation (EC) No 1831/2003)

 Renewal of a feed additive authorisation (Article 14 of Regulation (EC) No 1831/2003)

 Urgent authorisation (Article 15 of Regulation (EC) No 1831/2003)

(Please indicate clearly by ticking one of the boxes)

The Applicant(s) and/or his/their Representative(s) in the Community (Article 4(3) of Regulation (EC) No 1831/2003), under the conditions required in Article 7(3)(a) of Regulation (EC) No 1831/2003 (name, address….)

…

…

submit(s) the present application in order to obtain an authorisation for the following product as a feed additive:

1.1. Identification and characterisation of additive

Additive name (characterisation of the active substance(s) or agent(s) as defined in the subsections 2.2.1.1 and 2.2.1.2 of Annex II):

…

…

Trade name (if appropriate for the authorisations linked to the holder):

…

…

under the category/ies and functional group/s of additives [1] (list):

…

…

target species:

…

…

…

Name of the authorisation holder: (Article 9(6) of Regulation (EC) No 1831/2003)

…

…

This additive is already authorised in feed legislation by Directive …/…/(E)EC or Regulation (EC) No …/… under number … as (additive category)

…

This additive is already authorised in food legislation by Directive …/…/(E)EC or Regulation (EC) No …/… under number … as

…

for use in

…

If the product consists of, contains or is produced from a Genetically Modified Organism (GMO), please provide the following information:

 unique identifier (Commission Regulation (EC) No 65/2004 [2] (where appropriate):

…

 either the details of any authorisation granted in accordance with Regulation (EC) No 1829/2003 of the European Parliament and of the Council [3]:

…

 or the details of any pending application for authorisation under Regulation (EC) No 1829/2003:

…

1.2. Conditions of use

1.2.1. Use in complete feedingstuffs

Animal species or category:

…

…

Maximum age or weight:

…

…

Minimum dose (if appropriate): mg or Units of activity [4] or colony forming units (CFU) or ml/kg of complete feedingstuffs with a moisture content of 12 %

…

…

Maximum dose (if appropriate): mg or Units of activity or CFU or ml/kg of complete feedingstuffs with moisture content of 12 %

…

…

For liquid feeds the minimum and maximum doses can be expressed per litre.

1.2.2. Use in water

Minimum dose (if appropriate): mg or Units of activity or CFU or ml/l of water

…

…

Maximum dose (if appropriate): mg or Units of activity or CFU or ml/l of water

…

…

1.2.3. Special conditions of use (if appropriate)

Animal species or category:

…

…

Maximum age:

…

…

Minimum dose (if appropriate): mg or Units of activity or CFU/kg of complementary feedingstuffs with moisture content of 12 %

…

…

Maximum dose (if appropriate): mg or Units of activity or CFU/kg of complementary feedingstuffs with moisture content of 12 %

…

…

For liquid feeds the minimum and maximum doses can be expressed per litre.

Conditions or restrictions for use (if appropriate):

…

…

…

Specific conditions or restrictions for handling (if appropriate):

…

…

…

…

Maximum residue limit (if appropriate):

animal species or category:

…

…

marker residue:

…

…

target tissues or products:

…

…

…

Maximum residue in tissues or products (µg/kg):

…

…

…

Withdrawal period:

…

1.3. Reference samples

Community Reference Laboratory (CRL) sample number (if applicable):

…

Lot number/batch code:

…

Manufacturing date:

…

Expiry date:

…

Concentration:

…

Weight:

…

Physical description:

…

Container description:

…

Storage requirements:

…

1.4. Modification requested (where appropriate)

…

…

…

…

Copy of this application has been sent directly to the Authority with the dossier and to the CRL with the reference samples.

Signature …

1.5. Enclosures:

 complete dossier (only to the Authority);

 public summary of the dossier;

 detailed summary of the dossier;

 list of the parts of the dossier requested to be treated as confidential and a copy of the respective concerned parts of the dossier (only to Commission and Authority);

 copy of administrative data of applicant(s);

 three samples of the feed additive to the CRL following Article 7(3)(f) of Regulation (EC) No 1831/2003 (only to the CRL);

 material safety data sheet (only to the CRL);

 certificate of identification and analysis (only to the CRL); and

 confirmation that the fee to the CRL has been paid (Article 4 of Regulation (EC) No 378/2005 [5].

Complete the parts of the form where appropriate, and delete those parts that are not relevant. The original application form (with other enclosures requested) shall be sent directly to the European Commission.

2. ADMINISTRATIVE DATA OF APPLICANT(S)

Contact details for submitting an application for the authorisation of a feed additive under Regulation (EC) No 1831/2003

(1) Applicant company or person

(a) Name of the applicant or company

(b) Address (street, number, post code, city, country)

(c) Telephone

(d) Fax

(e) E-mail (if available)

(2) Contact person (for all correspondence with Commission, Authority and CRL)

(a) Name of contact person

(b) Position

(c) Address (street, number, post code, city, and country)

(d) Telephone

(e) Fax

(f) E-mail (if available)

[1] For the functional group "other zootechnical additives" under the category of zootechnical additives, it shall be necessary to define clearly which function is sought for the additive.

[2] OJ L 10, 16.1.2004, p. 5.

[3] OJ L 268, 18.10.2003, p. 1. Regulation as last amended by Regulation (EC) No 298/2008 (OJ L 97, 9.4.2008, p. 64).

[4] Definition of "Unit" shall be provided by the applicant.

[5] Commission Regulation (EC) No 378/2005 of 4 March 2005 on detailed rules for the implementation of Regulation (EC) No 1831/2003 of the European Parliament and of the Council as regards the duties and tasks of the Community Reference Laboratory concerning applications for authorisations of feed additives (OJ L 59, 5.3.2005, p. 8). Regulation as amended by Regulation (EC) No 850/2007 (OJ L 188, 20.7.2007, p. 3).

ANNEX II

GENERAL REQUIREMENTS TO BE SATISFIED BY THE DOSSIER PROVIDED FOR IN ARTICLE 3

GENERAL ASPECTS

This Annex sets out the requirements for establishing the list and the characteristics of studies and information on substances, micro-organisms and preparations to be submitted with dossiers under Article 7 of Regulation (EC) No 1831/2003 for:

- an authorisation as a new feed additive,

- an authorisation of a new use of a feed additive,

- a modification of an existing authorisation of a feed additive, or

- a renewal of the authorisation of a feed additive.

The dossiers must enable an assessment to be made of additives based on the current state of knowledge and permit verification of the compliance of these additives with the fundamental principles for authorisation, which are laid down in Article 5 of Regulation (EC) No 1831/2003.

The studies to be submitted and the extent of them will depend on the additive nature, the category and functional group, the type of authorisation (non-holder specific vs. holder specific), the substance itself, the target animals and the conditions of use. The applicant shall refer to this Annex and to Annex III in order to evaluate which studies and information shall be submitted with the application.

The applicant shall clearly provide the reasons for the omission or deviation from the dossier of any data prescribed in this Annex, Annex III and Annex IV.

The dossier shall include detailed reports of all the studies performed, presented in accordance with the numbering system proposed in this Annex. The dossier shall include references and copies of all published scientific data mentioned and the copies of any other relevant opinions which have already been produced by any recognised scientific body. Where these studies have already been evaluated by a European scientific body following the legislation in force in the Community, a reference to the result of the evaluation shall be sufficient. Data from studies that have been conducted

and published previously or coming from peer review shall clearly refer to the same additive as the one subject to the application for authorisation.

Studies, including those that have been conducted and published previously or coming from peer review, shall be performed and documented according to appropriate quality standards (e.g. Good Laboratory Practice (GLP)) in accordance with 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 [1] or International Organisation for Standardisation (ISO).

Where in vivo or in vitro studies are carried out outside the Community, the applicant shall demonstrate that the facilities concerned comply with the Organisation for Economic Cooperation and Development (OECD) principles of Good Laboratory Practice or ISO standards.

The determination of physico-chemical, toxicological and eco-toxicological properties must be performed in accordance with the methods established by Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances [2], as last amended by Commission Directive 2004/73/EC [3], or with updated methods recognised by international scientific bodies. The use of methods other than these must be justified.

The use of in vitro methods or of methods refining or replacing the usual tests using laboratory animals or reducing the number of animals used in these test shall be encouraged. Such methods shall be of the same quality and provide the same level of assurance as the method they aim to replace.

The description of the methods of analysis in feed or water shall be in conformity with the rules of GLP as laid down in Directive 2004/10/EC and/or EN ISO/IEC 17025. These methods shall comply with the requirements laid down in Article 11 of Regulation (EC) No 882/2004 of the European Parliament and of the Council of 29 April 2004 on official controls performed to ensure the verification of compliance with feed and food law, animal health and animal welfare rules [4].

Each dossier shall contain a public summary and a scientific detailed summary in order to enable the additive concerned to be identified and characterised.

Each dossier shall contain a post-market monitoring proposal where required by Article 7(3)(g) of Regulation (EC) No 1831/2003 and a labelling proposal as referred to in Article 7(3)(e) of Regulation (EC) No 1831/2003.

Safety assessment

This is based on studies intended to demonstrate the safety of the use of the additive in relation to:

(a) the target species at the highest proposed levels of incorporation in the feed or water and at a multiple of that level to establish a margin of safety;

(b) consumers who ingest food products obtained from animals that have received the additive, its residues or its metabolites. In this case, safety will be ensured by the setting of maximum residue limits (MRLs) and withdrawal periods based on an Acceptable Daily Intake (ADI) or an Tolerable Upper Intake Level (UL);

(c) persons likely to be exposed to the additive by respiratory, mucosal, eye or cutaneous contact while handling the additive or incorporating it into premixtures or complete feed or water or using feed or water containing the additive concerned;

(d) animals and humans with respect to the selection and spread of antimicrobial resistance genes; and

(e) the environment, as a result of the additive itself or products derived from the additive, either directly and/or as excreted by animals.

Where an additive has multiple components, each one may be separately assessed for consumer safety and then consideration given to the cumulative effect (where it can be shown that there are no interactions between the components). Alternatively, the complete mixture shall be assessed.

Efficacy assessment

This is based on studies that are intended to demonstrate the efficacy of an additive in terms of the aims of its intended use as defined in Article 6 (1) and Annex I of Regulation (EC) No 1831/2003.

1. SECTION I: SUMMARY OF THE DOSSIER

1.1. Public summary according to Article 7(3)(h) of Regulation (EC) No 1831/2003

The applicant shall submit a summary indicating the main features of the additive concerned. The summary shall not contain any confidential information and shall be structured as follows:

1.1.1. Contents

(a) name of the applicant(s);

(b) identification of the additive;

(c) method of production and method of analysis;

(d) studies on safety and efficacy of the additive;

(e) proposed conditions for use; and

(f) proposal for post-market monitoring.

1.1.2. Description

(a) name and address of the applicant(s)

This information shall be provided in all cases, independent of the type of feed additive authorisation (holder-specific or non-holder specific). When a dossier is submitted by a group of applicants, the name of each of them shall be indicated.

(b) identification of the additive

The identification of the additive shall contain a summary of the information required according to Annex II or III, depending on the type of the feed additive authorisation. In particular: name of the additive, proposed classification by category and functional group, target species/animal categories and doses.

(c) method of production and method of analysis

The manufacturing process shall be described.

The general procedures of the analytical methods to be used for the analysis for the official controls of the additive as such, in premixtures, and in feedingstuffs, as required in this Annex and Annex III shall be described. If appropriate, on the basis of the information submitted in this Annex and Annex III, the procedure of the

method(s) to be used for the analysis for the official controls of the additives or its metabolites in food of animal origin shall be included.

(d) studies on safety and efficacy of the additive

The conclusion regarding the safety and efficacy of the additive based on the different studies performed shall be given. The results of the studies may be included in a tabular form to support the conclusion of the applicant(s). Only studies required according to Annex III shall be indicated in the summary.

(e) proposed conditions for use

The proposal for conditions of use shall be provided by the applicant(s). In particular the applicant shall describe the level of use in water or feed, together with the detailed conditions of use in complementary feedingstuffs. Information is also required where other methods of administration or incorporation in feed or water are used. Any specific conditions for use (e.g. incompatibilities), specific labelling requirements and animal species for which the additive is intended shall be described.

(f) proposal for post-market monitoring

This part shall only relates to additives, which according to point (g) of Article 7(3) of Regulation (EC) No 1831/2003, do not belong to categories shown as (a) or (b) in Article 6(1) of the same Regulation and to additives falling within the scope of Community legislation relating to the marketing of products consisting of, containing or produced from GMOs.

1.2. Scientific summary of the dossier

A scientific summary including details of each part of the documents submitted to support the application, according to this Annex and Annex III shall be submitted. This summary shall include the conclusions made by the applicant(s).

The summary must follow the order of this Annex and address all the different parts with reference to the relevant pages of the dossier.

1.3. List of documents and other particulars

The applicant must identify the number and titles of volumes of documentation submitted in support of the application. A detailed index with reference to volumes and pages shall be added.

1.4. List of parts of the dossier requested to be treated as confidential, where necessary

The list shall make reference to the relevant volumes and pages of the dossier.

2. SECTION II: IDENTITY, CHARACTERISATION AND CONDITIONS OF USE OF THE ADDITIVE; METHODS OF ANALYSIS

The additive has to be fully identified and characterised.

2.1. Identity of the additive

2.1.1. Name of the additive

If appropriate, a proposal for the trade name shall be made for additives linked to a holder of authorisation.

2.1.2. Proposal for classification

A proposal for the classification of an additive for one or more categories and functional groups according to its main functions under Article 6 and Annex I of Regulation (EC) No 1831/2003 shall be made.

Any data from other known uses of the identical active substances or agents (e.g. use in food, human or veterinary medicine, agriculture and industry) must be provided. Any other authorisation as feed or food additive, veterinary drugs or other kind of authorisations of the active substance has to be specified.

2.1.3. Qualitative and quantitative composition (active substance/agent, other components, impurities, batch to batch variation)

The active substance(s)/agent(s) and all other components of the additive shall be listed, giving the proportion by weight in the final product. The qualitative and quantitative batch to batch variation of the active substance(s)/agent(s) shall be determined.

For micro-organisms: the number of viable cells or spores expressed as CFU per gram shall be determined.

For enzymes: each declared (main) activity shall be described and the number of units of each activity in the final product given. Relevant side activities shall be also mentioned. The units of activity shall be defined and preferably as μmoles of product released per minute from the substrate, also indicating the pH and the temperature.

If the active component of the additive is a mixture of active substances or agents, each of which is clearly definable (qualitatively and quantitatively), the active substance(s)/agent(s) components must be described separately and the proportions in the mixture given.

Other mixtures in which the constituents cannot be described by a single chemical formula and/or where not all can be identified shall be characterised by constituent(s) contributing to its activity and/or typical major constituent(s).

Without prejudice to any request of supplementary information made by the Authority according to Article 8(2) of Regulation (EC) No 1831/2003, the applicant may omit the description of other components with no safety concerns other than active substances or agents for additives not within the categories of zootechnical additives, coccidiostats and histomonostats, and not in the scope of Regulation (EC) No 1829/2003. In any case, all studies reported in the dossier must be based on the actual additive requested for the authorisation and may provide information on the other possible different preparations that could be made. An in-house identifier may be allowed, embedded in third-party documents, and a statement is required to list the identifiers and to confirm that the identifier(s) refers to the formulation(s) for which the request is made.

2.1.4. Purity

The applicant shall identify and quantify chemical and microbial impurities, substances with toxic or other undesirable properties that are not intentionally added and do not contribute to the activity of additive. In addition, for fermentation products, the applicant shall confirm the absence of production organisms in the additive. The protocol used for the routine screening of production batches for contaminants and impurities shall be described.

All the data provided have to support the proposal for a specification of the additive.

Specific requirements depending on the production process, complying with existing Community legislation, are listed below.

2.1.4.1. Additives whose authorisation is linked to a holder of authorisation

For additives whose authorisation is linked to a holder of authorisation, the relevant information related to the specific process used by the manufacturer, based on existing standards used for other related purposes, shall be provided. Joint FAO/WHO Expert Committee on Food Additives (JECFA) specifications or specifications from European Community food additive authorisations can be used.

2.1.4.2. Additives whose authorisation is not linked to a holder of authorisation

For feed additives whose authorisation is not linked to a holder of authorisation, existing standards used for other related purposes, or that have specifications for food additives as authorised in the European Community or from JECFA can be used. When such standards are not available, or where relevant to the manufacturing process, at least the following particulars shall be described and their concentrations determined:

- for micro-organisms: microbiological contamination, mycotoxins, heavy metals;

- for fermentation products (not containing micro-organisms as active agents): they shall follow the same requirements as for micro-organism products (see above). The extent to which spent growth medium is incorporated into the final product shall also be indicated.

- for plant derived substances: microbiological and botanical contamination (e.g. castor oil plant, weed seeds, rye ergot in particular), mycotoxins, pesticide contamination, maximum values for solvents and, where appropriate, substances of toxicological concern known to occur in the original plant;

- for animal derived substances: microbiological contamination, heavy metals and maximum values for solvents, where appropriate;

- for mineral substances: heavy metals, dioxins and PCBs;

- for products produced by chemical synthesis and processes: all chemicals used in the synthetic processes and any intermediate products remaining in the final product shall be identified and their concentrations given.

The selection of mycotoxins for analysis shall be made according to the different matrices, where appropriate.

2.1.5. Physical state of each form of the product

For solid preparations data on particle size distribution, particle shape, density, bulk density, dusting potential and the use of processes which affect physical properties shall be provided. For liquid preparations, data for viscosity and surface tension shall be given. Where additive is intended to be used in water, the solubility or extent of dispersion shall be demonstrated.

2.2. Characterisation of the active substance(s)/agent(s)

2.2.1. Description

A qualitative description of the active substance or agent shall be given. This shall include purity and origin of the substance or agent, plus any other relevant characteristics.

2.2.1.1. Chemical substances

Chemically well-defined substances shall be described by generic name, chemical name according to IUPAC (International Union of Pure and Applied Chemistry) nomenclature, other generic international names and abbreviations and/or Chemical Abstract Service Number (CAS). The structural and molecular formula and molecular weight must be included.

For chemically defined compound used as flavourings, the FLAVIS number in connection with relevant chemical group shall be included. For plant extracts the phytochemical markers must be included.

Mixtures in which the constituents cannot be described by a single chemical formula and/or not all of them can be identified shall be characterised by constituent(s) contributing to its activity and/or typical major constituent(s). Marker compound shall be identified to allow stability to be assessed and to provide a means of traceability.

For enzyme and enzyme preparations, the number and systematic name proposed by the International Union of Biochemistry (IUB) in the most recent edition of "Enzyme Nomenclature" shall be given for each declared activity. For activities not yet included, a systematic name consistent with the IUB rules of nomenclature shall be used. Trivial names are acceptable provided that they are unambiguous and used consistently throughout the dossier, and they can be clearly related to the systematic name and IUB number at their first mention. The biological origin of each enzyme activity must be given.

The microbial origin of chemical substances produced by fermentation shall also be described (see 2.2.1.2 Micro-organisms).

2.2.1.2. Micro-organisms

For all micro-organisms, whether used as product or as production strain, the origin shall be provided.

For micro-organisms used as a product or as production strain, any history of modification shall be indicated. The name and taxonomic classification of each micro-organism shall be provided, according to the latest published information in the International Codes of Nomenclature (ICN). Microbial strains shall be deposited in an internationally recognised culture collection (preferably in the European Union) and maintained by the culture collection for the authorised life of the additive. A certificate of deposition from the collection, which shall specify the accession number under which the strain is held, must be provided. In addition, all relevant morphological, physiological and molecular characteristics necessary to provide the unique identification of the strain and the means to confirm its genetic stability shall be described. For GMOs the description of the genetic modifications shall be given. The unique identifier for each GMO, as referred in Commission Regulation (EC) No 65/2004 of 14 January 2004 establishing a system for the development and assignment of unique identifiers for genetically modified organisms, shall be included.

2.2.2. Relevant properties

2.2.2.1. Chemical substances

Description of physical and chemical properties shall be given. Dissociation constant, pKa, electrostatic properties, melting point, boiling point, density, vapour pressure, solubility in water and in organic solvents, Kow and Kd/Koc, mass spectrometry and absorption spectra, NMR data, possible isomers and any other appropriate physical properties shall be provided, where appropriate.

Substance produced via fermentation shall be free of antimicrobial activities relevant to the use of antibiotics in humans or animals.

2.2.2.2. Micro-organisms

- Toxins and virulence factors

Toxins or virulence factors shall be demonstrated to be absent or of no concern. Strains of bacteria belonging to a taxonomic group that includes members known to be capable of producing toxins or other virulence factors shall be subject to appropriate tests to demonstrate at a molecular and, if necessary, cellular level the absence of any cause for concern.

For strains of micro-organisms for which there is no history of an apparent safe use and whose biology remains poorly understood, a full package of toxicological studies shall be necessary.

- Antibiotic production and antibiotic resistance

Micro-organisms used as additives or as production strain, shall be free of antibiotic activity or shall not be capable of producing antibiotic substances that are relevant as antibiotics in humans and animals.

Strains of micro-organisms intended for use as additives shall not contribute further to the reservoir of antibiotic resistance genes already present in the gut flora of animals and the environment. Consequently, all strains of bacteria shall be tested for resistance to antibiotics in use in human and veterinary medicine. Where resistance is detected, the genetic basis of the resistance and the likelihood of transfer of resistance to other gut-inhabiting organisms shall be established.

Strains of micro-organisms carrying an acquired resistance to antimicrobial(s) shall not be used as feed additives, unless it can be demonstrated that resistance is a result of chromosomal mutation(s) and it is not transferable.

2.3. Manufacturing process, including any specific processing procedures

To define the critical points of the process that may have an influence on the purity of the active substance/agent(s) or additive a description of the manufacturing process shall be given. A material safety data sheet of chemicals used in the production process shall be provided.

2.3.1. Active substance(s)/agent(s)

A description of the production process (e.g. chemical synthesis, fermentation, cultivation, extraction from organic material or distillation) used in the preparation of the active substance(s)/agent(s) of the additive shall be submitted, if appropriate by way of a flowchart. The composition of the fermentation/cultivation media shall be provided. Purification methods shall be thoroughly described.

For Genetically Modified Micro-organisms (GMMs), used as source of additives and grown under contained conditions, Council Directive 90/219/EC [5] applies. A description of fermentation processes (culture medium, fermentation condition and downstream processing of the fermentation products) shall be included.

2.3.2. Additive

A detailed description of the manufacturing process of the additive shall be submitted. The key stages in the preparation of the additive including the point(s) of introduction of the active substance(s)/agent(s) and other components, and any subsequent processing steps affecting the additive preparation should be provided, if appropriate by means of a flowchart.

2.4. Physico-chemical and technological properties of the additive

2.4.1. Stability

Stability is generally measured by the analytical follow-up of the active substance(s)/agent(s) or its activity/viability. For enzymes, stability may be defined in

terms of loss of catalytic activity; for micro-organisms in terms of loss of viability; for flavouring substances in terms of loss of flavour. For other chemical mixtures/extracts stability may be assessed by monitoring the concentration of one or more appropriate marker substances.

Stability of the additive

The stability of each formulation of the additive, on exposure to different environmental conditions (light, temperature, pH, moisture, oxygen and packing material) shall be studied. Expected shelf-life of the additive as marketed should be based on at least two model situations covering the likely range of use conditions (e.g., 25 oC, 60 % relative air humidity (HR) and 40 oC, 75 % HR).

Stability of the additive used in premixtures and feedingstuffs

For additives used in premixtures and in feedingstuffs, with the exception of flavouring compounds, the stability of each formulation of the additive shall be studied under common manufacturing and storage conditions of premixtures and of feedingstuffs. Stability studies in premixtures shall be of least six months' duration. Stability shall be tested preferably with premixtures containing trace elements; otherwise the additive should be labelled as "not to be mixed with trace elements".

Stability studies in feedingstuffs normally shall extend at least for three months. Generally stability shall be checked in mash and pelleted (including the influence of pelleting or other forms of treatment) feed for the main animal species of the claim.

For additives intended to be used in water, the stability of each formulation of the additive has to be studied in water under condition simulating practical use.

Where there is a loss of stability, and where appropriate, potential degradation or decomposition products shall be characterised.

Data shall be provided from analyses that include at least one observation at the beginning and one at the end of the storage period.

Where necessary, studies shall contain the detailed quantitative and qualitative composition of the premixtures or of the feedingstuffs used for the trials.

2.4.2. Homogeneity

The capacity for homogeneous distribution of the feed additive (other than flavouring compounds) in premixtures, feedingstuffs or water must be demonstrated.

2.4.3. Other characteristics

Other characteristics, such as dusting potential, electrostatic properties or dispersability in liquids must be described.

2.4.4. Physico-chemical incompatibilities or interactions

Physico-chemical incompatibilities or interactions that could be expected with feed, carriers, other approved additives, or medicinal products must be shown.

2.5. Conditions of use of the additive

2.5.1. Proposed mode of use in animal nutrition

The animal species or categories, age group or production stage of animals shall be indicated in accordance with the categories listed in Annex IV of this Regulation. Possible contra-indications shall be mentioned. The proposed use, in feed or water shall be defined.

Details of the proposed method of administration and level of inclusion must be provided for premixtures, feedingstuffs or water for drinking. In addition, the

proposed dose in the complete feed and the proposed duration of administration and proposed withdrawal period must be provided where appropriate. A justification is required where a particular use of an additive in complementary feedingstuffs is proposed.

2.5.2. Information related to users/workers safety

2.5.2.1. Chemical substances

A material safety data sheet formatted in accordance with the requirements of Commission Directive 91/155/EEC of 5 March 1991 defining and laying down the detailed arrangements for the system of specific information relating to dangerous preparations in implementation of Article 10 of Directive 88/379/EEC [6] must be provided. If necessary, measures for the prevention of occupational risks and means of protection during manufacture, handling, use and disposal shall be proposed.

2.5.2.2. Micro-organisms

A classification according to Directive 2000/54/EC of the European Parliament and of the Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work (seventh individual directive within the meaning of Article 16(1) of Directive 89/391/EEC) [7] shall be submitted. For micro-organisms not classified in group 1 in this Directive, information shall be provided to customers to allow them to take the relevant protection measures for their workers, as defined in Article 3 (2) of the said Directive.

2.5.2.3. Labelling requirements

Without prejudice to the labelling and packaging provisions laid down in Article 16 of Regulation (EC) No 1831/2003, any specific labelling requirements and, where appropriate, specific conditions for use and handling (including known incompatibilities and contraindications) and instructions for proper use shall be indicated.

2.6. Methods of analysis and reference samples

The methods of analysis shall be submitted in the standard layout as recommended by ISO (i.e. ISO 78-2).

According to Regulation (EC) No 1831/2003 and Regulation (EC) No 378/2005, methods of analysis included in this section shall be evaluated by the CRL. The CRL shall submit to the Authority an evaluation report indicating whether these methods are suitable to be used for official controls of the feed additive that is the object of the application. The CRL evaluation shall focus on the methods specified in sections 2.6.1 and 2.6.2.

If an MRL has been established for the substance object of the application by Council Regulation (EEC) No 2377/90 of 26 June 1990 laying down a Community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin [8], section 2.6.2 will not be subject to evaluation by the CRL. The applicant shall compile section 2.6.2 providing the same method, information and particulars (including relevant updates) for submission to European Medicines Agency (EMEA) in accordance with Annex V of Regulation (EEC) No 2377/90 and in accordance with "Notice to Applicants and Guidelines", Volume 8 of the series "Rules governing medicinal products in the European Union".

Analytical methods described under 2.6.3 may also be included in the evaluation, if considered necessary by the CRL, the Authority or the Commission.

In accordance with Regulation (EC) No 378/2005, the applicant shall provide reference samples directly to the CRL prior to the evaluation of the technical dossier, and replacement samples before the expiration date.

Applicants shall refer to the detailed guidance provided by the CRL in accordance with Article 12 of Regulation (EC) No 378/2005.

2.6.1. Methods of analysis for the active substance

Detailed characterisation of the qualitative and, where applicable, quantitative analytical method(s) for determining compliance with maximum or minimum proposed levels of the active substance(s)/agent(s) in the additive, premixtures, feedingstuffs and, when appropriate, water, shall be provided.

2.6.1.1. These methods shall meet the same requirements as those for methods of analysis used for official control purpose laid down in Article 11 of Regulation (EC) No 882/2004 In particular they shall meet at least one of the following requirements:

- comply with relevant Community rules (e.g. Community methods of analysis) where they exist;

- comply with internationally recognised rules or protocols, for example those that the European Committee for Standardisation (CEN) has accepted, or those agreed in national legislation (e.g. CEN Standard methods);

- are fit for the intended purpose, developed in accordance with scientific protocols and validated in a ring test in accordance with an internationally recognised protocol on collaborative trials (e.g. ISO 5725 or IUPAC); or

- are validated in-house according to international harmonised guidelines for the in-house validation of methods of analysis [9] with respect to the characterising parameters mentioned in 2.6.1.2.

2.6.1.2. The detailed characterisation of the method(s) shall include the appropriate characteristics set out in Annex III of Regulation (EC) No 882/2004.

2.6.1.3. Performance characteristics of in-house validated methods shall be verified by testing the method in a second, accredited and independent laboratory. Results of such tests shall be provided together with any other information supporting the transferability of the method to an official control laboratory. For reasons of independence and involvement in the evaluation of the documentation provided by the applicant, where the second laboratory is a laboratory participating in the consortium of National Reference Laboratories (NRLs) assisting the CRL, as laid down in Regulation (EC) No 378/2005, the laboratory shall send a declaration of interests to the CRL, as soon as the application is received by the CRL, describing the work of the laboratory in the application and shall not participate in the evaluation of the application.

2.6.1.4. The CRL may select appropriate characteristics as mentioned under Annex III of Regulation (EC) No 882/2004 in its evaluation report to the Authority.

2.6.1.5. Performance criteria for methods for specific groups of substances (e.g. enzymes) may be established in the detailed guidance provided by the CRL in accordance with Article 12 of Regulation (EC) No 378/2005.

2.6.2. Methods of analysis for the determination of the residues of the additive or of its metabolites in food

Detailed characterisation of the qualitative and quantitative analytical method(s) for determining the marker residues and/or metabolites of the additive in target tissues and animal products shall be provided.

2.6.2.1. These methods shall meet the same requirements as those for methods of analysis used for official control purposes as laid down in Article 11 of Regulation (EC) No 882/2004. In particular, the methods shall meet at least one of the requirements mentioned in 2.6.1.1.

2.6.2.2. The detailed characterisation of the method(s) shall include the appropriate characteristics as set out in Annex III of Regulation (EC) No 882/2004 and shall take into account the requirements set out in Commission Decision 2002/657/EC [10]. The same performance criteria laid down in Commission Decisions laying down analytical methods to be used for detecting certain substances and residues thereof in live animal products according to Council Directive 96/23/EC shall be considered where appropriate.

The limit of quantification (LOQ) for each method must not exceed half of the corresponding MRL and must be validated across a range at least from one-half to two times the MRL.

2.6.2.3. Performance characteristics of in-house validated methods shall be verified by testing the method in a second, accredited and independent laboratory. Results of such tests shall be provided. For reasons of independence and involvement in the evaluation of the documentation provided by the applicant, where the second laboratory is a laboratory participating in the consortium of National Reference Laboratories (NRLs) assisting the CRL, as laid down in Regulation (EC) No 378/2005, the laboratory shall send a declaration of interests to the CRL, as soon as the application is received by the CRL, describing the work of the laboratory in the application and shall not participate in the evaluation of the application.

2.6.2.4. The CRL may select appropriate characteristics from the ones mentioned under point 2.6.2.2 in its evaluation report to the Authority.

2.6.2.5. Performance criteria for methods for specific groups of substances (e.g. enzymes) may be established in the detailed guidance provided by the CRL in accordance with Article 12 of Regulation (EC) No 378/2005.

2.6.3. Methods of the analysis relating to the identity and characterisation of the additive

A description of the methods used for the determination of the characteristics listed under points 2.1.3, 2.1.4, 2.1.5, 2.2.2, 2.4.1, 2.4.2, 2.4.3, and 2.4.4 shall be provided by the applicant.

In accordance with Annex II of Regulation (EC) No 1831/2003 as amended by Regulation (EC) No 378/2005, the methods submitted under this section may also be evaluated if considered relevant by the, the Authority or the Commission for the assessment of the application.

It is recommended that the methods described under this section are internationally recognised. For those methods that are not internationally recognised, the methods have to be fully described. In those cases, studies shall be performed by accredited and independent laboratories and shall be documented according to appropriate quality standards (e.g. GLP in accordance with Directive 2004/10/EC or ISO standards).

Methods for the identification and characterisation of the additive shall meet the same requirements as those for methods of analysis used for official control purposes as laid

down in Article 11 of Regulation (EC) No 882/2004, particularly where legal requirements are established (e.g. impurities, undesirable substances).

3. SECTION III: STUDIES CONCERNING SAFETY OF THE ADDITIVE

The studies included in this section and in the specific Annexes are intended to permit assessment of:

- the safety of use of the additive in the target species;

- any risk associated with the selection and/or transfer of resistance to antimicrobials and increased persistence and shedding of enteropathogens;

- the risks to the consumer of food derived from animals given feedingstuffs containing or treated with the additive or which could result from the consumption of food containing residues of the additive or its metabolites;

- the risks from respiratory, other mucosal tissue, eye or cutaneous contact for persons likely to handle the additive as such or as incorporated into premixtures or feedingstuffs; and

- the risks of adverse effects on the environment, from the additive itself, or from products derived from the additive, either directly and/or excreted by animals.

3.1. Studies concerning the safety of use of the additive for the target animals

The studies included in this section are intended to assess:

- the safety of use of the additive in the target species per se; and

- any risk associated with the selection and/or transfer of resistance to antimicrobials and increased persistence and shedding of enteropathogens.

3.1.1. Tolerance studies for the target species

The aim of the tolerance test is to provide a limited evaluation of short-term toxicity of the additive to the target animals. It is also used to establish a margin of safety, if the additive is consumed at higher doses than recommended. Such tolerance tests must be conducted to provide evidence for safety for each of the target species/animal categories for which a claim is made. In some cases it is acceptable to include some elements of the tolerance test in one of the efficacy trials provided that the requirements given below for these tests are met. All studies reported in this section must be based on the additive described in Section II.

3.1.1.1. The design of a tolerance test includes a minimum of three groups:

- an unsupplemented group;

- a group with the highest recommended dose; and

- an experimental group with the multi-fold level of the highest recommended dose.

In the experimental group the additive shall generally be given at ten times the highest recommended dose. Test animals shall be routinely monitored for visual evidence of clinical effects, performance characteristics, product quality where relevant, haematology and routine blood chemistry and for other parameters likely to be related to the biological properties of the additive. Critical end-points known from the toxicological studies in laboratory animals shall be considered. Any adverse effect detected during efficacy trials shall also be reported in this section. Unexplained deaths in the tolerance test shall be investigated by necropsy and, if appropriate, histology.

If a 100 times the maximum recommended dose can be shown to be tolerated, no haematology or routine blood chemistry would be required. If the product is tolerated only at lower level than ten times of the highest recommended dose, the study shall be

designed in such a way that a margin of safety for the additive can be calculated and additional end-points (by necropsy, histology if relevant, and other appropriate criteria) shall be provided.

For some additives depending on their toxicology and metabolism or use, it may not be necessary to carry out tolerance tests.

The experimental design used must include consideration of adequate statistical power.

3.1.1.2. Duration of tolerance trials

Table 1

Duration of tolerance trials: Pigs

Target animals | Duration of the studies | Characteristic of the target animals |

Suckling piglets | 14 days | Preferably from 14 days to weaning |

Weaned piglets | 42 days | For 42 days after weaning |

Pigs for fattening | 42 days | Body weight at start of the study ≤ 35 kg |

Sows for reproduction | 1 cycle | From insemination to the end of the weaning period |

If suckling and weaned piglets are applied for, a combined study (14 days suckling piglets and 28 days weaned piglets) would be considered sufficient. If the tolerance for weaned piglets has been shown, no separate study for pigs for fattening is required.

Table 2

Duration of tolerance trials: Poultry

Target animals | Duration of the studies | Characteristic of the target animals |

Chickens for fattening/reared for laying | 35 days | From hatching |

Laying hens | 56 days | Preferably during the first third of the laying period |

Turkeys for fattening | 42 days | From hatching |

Tolerance data from chickens for fattening or turkeys for fattening can be used to demonstrate tolerance for chickens or turkeys reared for laying/breeding respectively.

Table 3

Duration of tolerance trials: Bovines

Target animals | Duration of the studies | Characteristic of the target animals |

Calves for fattening | 28 days | Initial bodyweight ≤ 70kg |

Calves for rearing; cattle for fattening or reproduction | 42 days | |

Dairy cows | 56 days | |

If calves for rearing and cattle for fattening were applied for, a combined study (28 days for each period) would be considered sufficient.

Table 4

Duration of tolerance trials: Sheep

Target animals | Duration of the studies | Characteristic of the target animals |

Lambs for rearing and for fattening | 28 days | |

Table 5

Duration of tolerance trials: Salmonidae and other fish

Target animals | Duration of the studies | Characteristic of the target animals |

Salmon and trout | 90 days | |

As an alternative to a 90-day duration, a study could be performed where the fish increase their initial body weight at the start of the trial by least a factor of two.

If the additive is intended to be used for brood stock only, the tolerance tests shall be carried out as close to the spawning period as possible. The tolerance tests shall last for 90 days and attention shall be paid to the egg quality and survival of the eggs.

Table 6

Duration of tolerance trials: Pets and other non food-producing animals

Target animals | Duration of the studies | Characteristic of the target animals |

Dogs and cats | 28 days | |

Table 7

Duration of tolerance trials: Rabbits

Target animals | Duration of the studies | Characteristic of the target animals |

Rabbits for fattening | 28 days | |

Breeding does | 1 cycle | From insemination to the end of the weaning period |

If rabbits suckling and weaned are applied for, a period of 49 days (beginning one week after birth) would be considered sufficient and must include the does until weaning.

If an additive is applied for a specific and shorter period than given by the animal category definition, it shall be administered according to the proposed conditions of use. However, the observation period shall not be shorter than 28 days and shall involve the relevant end-point (e.g. for sows for reproduction the number of piglets born alive when considering the gestation period, or the number and weight of weaned piglets when considering the lactation period).

3.1.1.3. Experimental conditions

The studies shall be reported individually, giving details of all experimental groups. The trial protocol shall be carefully drawn up with regard to general descriptive data. In particular, the following shall be recorded:

(1) herd or flock: location and size; feeding and rearing conditions, method of feeding; for aquatic species, size and number of tanks or pens at the farm, light conditions and water quality including water temperature and salinity;

(2) animals: species (for aquatic species intended for human consumption identification shall be made by their colloquial name followed in parenthesis by the Latin binomial), breed, age (size for aquatic species), sex, identification procedure, physiological stage and general health;

(3) date and exact duration of testing: date and nature of the examinations performed;

(4) diets: description of manufacture and quantitative composition of the diet(s) in terms of ingredients used, relevant nutrients (analysed values) and energy. Feed intake records;

(5) concentration of the active substance(s) or agent(s) (and, where that is the case, substances used for comparative purposes) in the feedingstuffs shall be established by a control analysis, using the appropriate recognised methods: reference number(s) of the batches;

(6) number of test and control groups, number of animals in each group: the number of animals involved in the trials must permit statistical analysis. The methods of statistical evaluation used should be stated. The report shall include all animals and/or

experimental units involved in the trials. Cases which cannot be assessed due to a lack or loss of data shall be reported, and their distribution within the groups of animals classified;

(7) the timing and prevalence of any undesirable consequences of treatment in individuals or groups must be reported (give details of the observation programme used in the study); and

(8) therapeutic/preventive treatments, if necessary, shall not interact with the proposed mode of action of the additive and shall be recorded individually.

3.1.2. Microbial studies

Studies shall be provided to determine the ability of the additive to induce cross-resistance to antibiotics used in human or veterinary medicine, to select resistant bacterial strains under field conditions in target species, to give rise to effects on opportunistic pathogens present in the digestive tract, to cause shedding or to excrete zoonotic micro-organisms.

If the active substance(s) possesses antimicrobial activity at the feed concentration level, the minimum inhibitory concentration (MIC) for relevant bacterial species shall be determined, according to standardised procedures. Where relevant antimicrobial activity is demonstrated, the ability of the additive to select resistant bacterial strains in vitro and in the target species, and to induce cross-resistance to relevant antibiotics shall be established [11].

Tests at the recommended use level shall be provided for all microbial additives, and for those other additives in which an effect on the gut micro-flora can be anticipated. These studies shall demonstrate that use of the additive does not create conditions conducive to an overgrowth and shedding of potentially pathogenic micro-organisms.

The choice of micro-organisms to be monitored will depend on the target species, but shall include relevant zoonotic species, regardless of whether or not they produce symptoms in target animals.

3.2. Studies concerning the safety of use of the additive for consumers

The aim is to evaluate the safety of the additive for the consumer and to establish potential residues of the additive or its metabolites in food derived from animals given feed or water containing or treated with the additive.

3.2.1. Metabolic and residue studies

The establishment of the metabolic fate of the additive in the target species is a determinant step in the identification and quantification of the residues in the edible tissues or products derived from the animals given the feed or water containing the additive. Studies must be submitted concerning the absorption, distribution, metabolism and excretion of the substance (and its metabolites).

Studies must be carried out using internationally validated test methods and shall be performed in accordance with European legislation in force or OECD Guidelines for methodological details and according to the principles of GLP. The study shall respect the rules on animal welfare laid down by European Community legislation, and they shall not be repeated if not necessary.

Metabolic and residue studies on the target animal(s) shall be performed with the active substance incorporated in the feed (not given by gavage unless it is properly justified).

Structural identification of metabolites representing more than 10 % of the total residues in the edible tissues and products and more than 20 % of the total residues in the excreta shall be established. If the metabolic pathway of the active substance raises any toxicological concerns, metabolites below the above limits shall be identified.

Kinetic studies of the residues will form the basis for the calculation of consumer exposure and the establishment of a withdrawal period and MRLs, if necessary. A proposal for a marker residue shall be provided.

For some additives, depending on their nature or use, it may not always be necessary to carry out metabolic and residues studies.

3.2.1.1. Metabolic studies

The purpose of metabolic studies is to evaluate the absorption, distribution, biotransformation and excretion of the additive in the target species.

The studies required are:

(1) metabolic balance following a single dose administration of the active substance at the doses proposed for use (total amount corresponding to the daily intake) and possibly a multiple dose (if justified) to assess an approximate rate and extent of the absorption, distribution (plasma/blood) and excretion (urine, bile, faeces, milk or eggs, expired air, excretion via gills) in male and female animals, where appropriate; and

(2) metabolic profiling, identification of the metabolite(s) in excreta and tissues and distribution in tissues and products shall be established following repeated dose administration of the labelled compound to animals to the steady state (metabolic equilibrium) identified by plasma levels. The dose applied shall correspond to the highest dose proposed for use, and shall be incorporated into the feed.

3.2.1.2. Residue studies

Consideration shall be given to the amount and the nature of non-extractable residues in edible tissues or products.

Residue studies are required for all substances for which metabolic studies are needed.

If the substance is a natural constituent of body fluids or tissues or is naturally present in significant amounts in food or feedingstuffs, the requirement for residue studies is limited to the comparison of the tissue/product levels in an untreated group and in the group supplemented with the highest dose claimed.

For major species, studies shall simultaneously evaluate the total residues of toxicological significance and identify the marker residue of the active substance in edible tissue (liver, kidney, muscle, skin, skin + fat) and products (milk, eggs and honey). The marker residue is the residue selected for assay whose concentration has a known relationship to the total residue of toxicological concern in the tissues. Studies shall also show the permanence of the residues in the tissues or products to establish an appropriate withdrawal period.

For the determination of a withdrawal period, the suggested minimum number of animals sampled and/or products at each time point are the following:

- edible tissues:

- bovines, sheep, pigs and minor species 4;

- poultry 6;

- salmonids and other fish 10.

- products:

- milk 8 samples per time point;

- eggs 10 eggs per time point;

- honey 8 samples per time point.

Appropriate sex distribution shall be considered.

The residues shall be measured at zero withdrawal time (steady state) and at least three other time sampling points.

A proposal for a marker residue shall be provided.

Studies on the absorption, distribution and excretion, including the identification of main metabolites must be performed in the laboratory animal species in which the lowest NOAEL was obtained, or by default in the rat (both sexes). Additional studies on particular metabolites may be necessary if these metabolites are produced by target species and are not formed to a significant extent in the laboratory species.

3.2.1.3. Metabolic and disposition studies

A metabolism study including the metabolic balance, metabolic profile and identification of the main metabolites in the urine and faeces shall be performed. If another laboratory species shows a marked difference in the sensitivity from the rat, additional information will be required.

3.2.1.4. Bioavailability of residues

The assessment of the risks for the consumers related to bound residues in animal products may take into account an additional safety factor on the determination of their bioavailability using appropriate laboratory animals and recognised methods.

3.2.2. Toxicological studies

The safety of the additive is assessed on the basis of the toxicological studies performed in vitro and in vivo on laboratory animals. They generally include measurements of:

(1) acute toxicity;

(2) genotoxicity (mutagenicity, clastogenicity);

(3) sub-chronic oral toxicity;

(4) chronic oral toxicity/carcinogenicity;

(5) reproduction toxicity including teratogenicity; and

(6) other studies.

Further studies providing additional information necessary for the assessment of the safety of the active substance and its residues shall be conducted if there is any reason for concern.

On the basis of the results of these studies a toxicological NOAEL must be established.

Additional studies on particular metabolites may be necessary if these metabolites are produced by target species and are not formed to a significant extent in the laboratory test species. If metabolic studies are available in humans, data shall be taken into consideration in deciding the nature of eventual additional studies.

Toxicological studies must be carried out with the active substance. If the active substance is present in a fermentation product, the fermentation product shall be tested. The fermentation product tested must be identical to that to be used in the commercial product.

Studies must be carried out using internationally validated test methods and shall be performed in accordance with European legislation in force or OECD Guidelines for

methodological details and according to the principles of GLP. The studies involving laboratory animals shall respect the rules on animal welfare laid down by European legislation and they shall not be repeated if not necessary.

3.2.2.1. Acute toxicity

Acute toxicity studies are required to classify and to provide limited characterisation of the toxicity of the compound.

Acute toxicity studies shall be carried out in at least two mammalian species. One laboratory species may be replaced by a target species, if appropriate.

It will be not necessary to determine a precise LD50; an approximate determination of the minimum lethal dose is considered sufficient. The maximum dosage shall not exceed 2000 mg/kg body weight.

In order to reduce the number and the suffering of the animals involved, new protocols for acute dose toxicity testing are continually being developed. Studies carried out by these new procedures will be accepted, when properly validated.

OECD Guidelines 402 (acute dermal toxicity), 420 (Fixed Dose Method), 423 (Acute Toxic Class Method) and 425 (Up-and-Down Procedure) should be followed.

3.2.2.2. Genotoxicity studies including mutagenicity

To identify active substances and, if appropriate, their metabolites and degradation products with mutagenic and genotoxic properties, a selected combination of different genotoxicity tests must be carried out. If appropriate the tests shall be performed without and with mammalian metabolic activation and the compatibility of the test material with the test system shall be taken into account.

The core set comprises the following tests:

(1) induction of gene mutations in bacteria and/or in mammalian cells (preferably the mouse lymphoma tk assay);

(2) induction of chromosomal aberrations in mammalian cells; and

(3) in vivo test in mammalian species.

Additional tests may be needed depending on the outcome of the above mentioned tests and taking into consideration the whole toxicity profile of the substance, as well as its intended use.

Protocols should be in line with OECD Guideline 471 (Salmonella typhimurium Reverse Mutation Test), 472 (Escherichia coli Reverse Mutation Test), 473 (in vitro Mammalian Chromosomal Aberration Test), 474 (Mammalian Erythrocyte Micronucleus Test), 475 (Mammalian Bone Marrow Chromosomal Aberration Test), 476 (in vitro Mammalian Cell Gene Mutation Test) or 482 (Unscheduled DNA Synthesis in Mammalian Cells in vitro), as well as other relevant OECD Guidelines for in vitro and in vivo assays.

3.2.2.3. Sub-chronic repeated dose oral toxicity studies

To investigate the sub-chronic toxic potential of the active substance, at least one study on a rodent species must be submitted with duration of at least 90 days. If deemed necessary, a second study must be performed with a non-rodent species. The test item must be administered orally with at least three levels in addition to a control group to obtain a dose response. The maximum dose used should normally be expected to reveal evidence of adverse effects. The lowest dose level should not be expected to produce any evidence of toxicity.

Protocols for these studies should be in line with the OECD Guidelines 408 (rodents) or 409 (non-rodents).

3.2.2.4. Chronic oral toxicity studies (including carcinogenicity studies)

To investigate the chronic toxic potential and carcinogenic potential, a chronic oral toxicity study must be carried out in at least one species, and shall be of at least 12 months' duration. The species chosen shall be the most appropriate on the basis of all available scientific data, including the results of the 90-day studies. The default species is the rat. If a second study is requested, a rodent or a non-rodent mammalian species shall be used. The test item must be administered orally with at least three levels in addition to a control group to obtain a dose response.

If the chronic toxicity study is combined with an examination of carcinogenicity, then the duration shall be extended to 18 months for mice and hamsters, and to 24 months for rats.

Carcinogenicity studies may not be necessary if the active substance and its metabolites:

(1) give consistently negative results in the genotoxicity tests;

(2) are not structurally related to known carcinogens; and

(3) give no effects indicative of potential (pre)neoplasia in chronic toxicity assays.

Protocols should be in line with OECD Guideline 452 (chronic toxicity study) or 453 (combined chronic toxicity/carcinogenicity study).

3.2.2.5. Reproduction toxicity studies (including prenatal developmental toxicity)

To identify possible impairment of male or female reproductive function or harmful effects on progeny resulting from the administration of the active substance, studies of reproductive function must be carried out by:

(1) two generation reproduction toxicity study; and

(2) prenatal developmental toxicity study (teratogenicity study).

For new trials validated alternative methods reducing the use of animals can be used.

3.2.2.5.1. Two generation reproduction toxicity study

Studies of reproductive function must be carried out and extend over at least two filial generations (F1, F2) in at least one species, usually a rodent, and may be combined with a teratogenicity study. The substance under investigation shall be administered orally to males and females at an appropriate time prior to mating. Administration shall continue until the weaning of the F2 generation.

All relevant fertility, gestation, parturition, maternal behaviour, suckling, growth and development of the F1 offspring from fertilisation to maturity and the development of the F2 offspring to weaning must be carefully observed and reported. Protocols for the reproduction toxicity study should be in line with OECD Guideline 416.

3.2.2.5.2. Prenatal developmental toxicity study (teratogenicity study)

The objective is to detect any adverse effects on the pregnant female and the development of the embryo and foetus as a result of exposure from implantation through the entire gestation period. Such effects include enhanced toxicity in the pregnant females, embryo-foetal death, altered foetal growth and structural abnormalities and anomalies in the foetus.

The rat is usually the species of choice for the first study. If a negative or an equivocal result for teratogenicity is observed, another developmental toxicity study shall be

conducted in a second species, preferably the rabbit. If the rat study is positive for teratogenicity, a study in a second species is not necessary except where a review of all the core studies indicates that the ADI would be based on the rat teratogenicity. In this case a study in a second species would be required to determine the most sensitive species for this endpoint. Protocols should be in line with OECD Guideline 414.

3.2.2.6. Other specific toxicological and pharmacological studies

Further studies providing additional information useful for the assessment of the safety of the active substance and its residues shall be conducted if there are reasons for concern. Such studies may include examination of pharmacological effects, effects in juvenile (prepubertal) animals, immunotoxicity or neurotoxicity.

3.2.2.7. Determination of No Observed Adverse Effect Levels (NOAEL)

The NOAEL is generally based on toxicological effects, but pharmacological effects might occasionally be more appropriate.

The lowest NOAEL shall be selected. All findings from previous sections together with all other relevant published data (including any relevant information on the effects of the active substance on human) and information, where appropriate, on chemicals having a closely related chemical structure shall be taken into consideration in identifying the lowest NOAEL, expressed as mg per kg body weight per day.

3.2.3. Assessment of consumer safety

Consumer safety is assessed by a comparison of the established ADI (Acceptable Daily Intake) and calculated theoretical intake of the additive or its metabolites from food. In the case of vitamins and trace elements, UL (Tolerable Upper Intake Level) can be used in place of ADI.

3.2.3.1. Proposal of the acceptable daily intake (ADI) for the active substance(s)

The acceptable daily intake (ADI) (expressed as mg of additive or additive related material per person per day) is derived by dividing the lowest NOAEL (mg per kg body weight) by an appropriate safety factor and multiplying by the average human body weight of 60 kg.

An ADI shall, where appropriate, be proposed. An ADI can also be "not specified" because of low toxicity in animal tests. An ADI shall not be proposed if the substance shows genotoxic or carcinogenic properties relevant to humans.

The setting of an ADI normally requires the similarity of metabolic fate of the active substance in the target animals and laboratory animals (see 3.2.1.4 Bioavailability of residues) which ensures that consumers are exposed to the same residues as the laboratory animals used in toxicological studies. If not, additional studies in a second laboratory animal species or with the metabolites specific to the target species may still allow an ADI to be set.

The safety factor used to determine the ADI for a particular additive will take into consideration the nature of the biological effects and the quality of the data used to identify the NOAEL, the relevance of these effects to man and their reversibility and any knowledge of the direct effect(s) of the residues in human.

A safety factor of at least 100 in calculating the ADI (if a full toxicological package has been provided) shall be employed. Where data on the active substance are available for human, a lower safety factor may be acceptable. Higher safety factors might be applied to account for additional sources of uncertainty in data or where the NOAEL is set on the basis of a particular critical endpoint, such as teratogenicity.

3.2.3.2. Tolerable upper intake level (UL)

For some additives it may be more appropriate to base the safety assessment on the UL, which is the maximum level of total chronic daily intake of a nutrient (from all sources) judged (by national or international scientific bodies) to be unlikely to pose a risk of adverse health effects to consumers or to specific groups of consumers.

The dossier shall contain data to demonstrate that use of the additive would not lead to a situation in which the UL could be exceeded considering all possible sources of the nutrient.

If the resulting residue levels of the nutritional additive or its metabolite(s) in products of animal origin are higher than what is considered normal or expected for these products, this shall be clearly indicated.

3.2.3.3. Consumer exposure

The total intake of the additive and/or its metabolites from all sources by the consumer shall be below the ADI or UL.

Calculation of the theoretical intake from food of animal origin shall be performed considering the concentration (total residues as the arithmetic mean and the highest single value) measured in tissues and products at the termination of use of the additive. In addition, if necessary, at the different withdrawal times, the human daily food consumption values shall be determined following a worst case scenario.

For additives intended for multi-species, the exposure from tissues shall be independently calculated for mammals, birds and fish and the highest value taken. Where appropriate, exposure from milk and eggs shall be added to this figure. For example, where an additive is applied for lactating mammals and laying birds, the respective highest edible tissue values are added to those for milk and egg consumption. Where the additive is applied for fish and laying birds and lactating mammals, the respective highest edible tissue values are added to those for egg and milk consumption. Other combinations shall be envisaged in the same way.

In certain situations (e.g. some nutritional and sensory additives or additives intended for minor species) it may be appropriate to subsequently refine the human exposure assessment using more realistic consumption figures, but still keeping the most conservative approach. Where this is possible this shall be based on Community data.

Table 1

Theoretical daily human consumption figures (g tissues or products)

| Mammals | Birds | Fish | Other |

Muscle | 300 | 300 | 300 [] | |

Liver | 100 | 100 | — | |

Kidney | 50 | 10 | — | |

Fat | 50 [] | 90 [] | — | |

+ Milk | 1500 | — | — | |

+ Eggs | — | 100 | — | |

+ Honey | | | | 20 |

3.2.3.4. Proposal for maximum residue limits (MRLs)

Maximum residue limit means the maximum concentration of residues (expressed as µg marker residue per kg of edible wet tissue or product) which may be accepted by the Community to be legally permitted or recognised as acceptable in food. It is based

on the type and amount of residue considered to be without any toxicological hazard for human health as expressed by the ADI. An MRL cannot be set in the absence of an ADI.

When establishing MRLs for feed additives, consideration is also given to residues that come from other sources (e.g., food of plant origin). Furthermore, the MRL may be reduced to be consistent with the conditions of use of feed additives and to the extent that practical analytical methods are available.

Where appropriate, individual MRLs (expressed as mg marker residue per kg of edible natural tissue or product) shall be set for different tissues or products of the target animal species. The individual MRLs in different tissues or products shall reflect the depletion kinetics and the variability of the residue levels within those tissues/products in the animal species intended for use. Variability shall normally be reflected by using the 95 % confidence limit of the mean. If the confidence limit cannot be calculated due to a low number of samples, variability is expressed by taking the highest individual value instead.

Studies concerning the Maximum Residue Limits of coccidiostats and histomonostats must be carried out following the appropriate rules in force for veterinary medicinal products (Volume 8 "The rules governing medicinal products in European Union — Notice to applicants and guidelines. Veterinary medicinal products. Establishment of maximum residue limits (MRLs) for residues of veterinary medicinal products in foodstuffs of animal origin". October 2005).

The studies to establish maximum residue limits for additive categories other than coccidiostats and histomonostats, where necessary, shall be provided according to this Annex.

To determine the consumer exposure to the total residues (as calculated under 3.2.3.3.), the proposed MRLs for the different tissues or products shall take into account the ratio of marker residue to total residue (Table 2).

Table 2

Definitions used in deriving an MRL

i-j | Individual tissues/products (liver, kidney, muscle, skin + fat, milk, eggs, honey) at different times |

MRLi-j | Maximum residue limit in tissues/products (mg marker substance kg-1) |

Qti-j | Daily human consumption of individual tissues/products (kg) set by Table 1 or its refinement |

TRCi-j | Total residue concentration in individual tissues/products (mg kg-1) |

MRCi-j | Marker residue concentration in individual tissues/products (mg kg-1) |

RMTRi-j | Ratio MRCi-j to TRCi-j for individual tissues/products |

DITRi-j | Dietary intake for individual tissues/products calculated from total residues (mg) DITRi-j = Qti-j x TRCi-j |

DITRMRLi-j | Dietary intake calculated from MRLs (mg) of individual tissues/products DITRMRLi-j = Qti-j x MRLi-j x RMTRi-j-1 |

The measured values for TRC and MRC shall be inserted as appropriate in the template shown in Table 3, and the other values calculated. Where a full data set is not available because values fall below the limit of detection (LOD), an extrapolation of RMTR may be acceptable.

Deriving an MRL can only be performed if the sum of the individual DITRs is below the ADI. If the ADI is exceeded, an alternative would be to use data from a longer withdrawal time or lower dosages. A first proposal for an MRL can be obtained using the MRC value as a guide and taking into consideration the LOQ of the analytical method. The sum of the DITRMRL obtained from the proposed MRLs must be below the ADI and close to the sum of the individual DITRs. If the ADI is exceeded, then a lower MRL shall be proposed and the comparison repeated.

For certain additives, residues could arise below the MRL values in milk, eggs or meat which could nonetheless interfere with food quality in particular food processing procedures. For such additives, it may be appropriate to consider a "maximum (food product) processing compatible residue" (MPCR) in addition to establishing MRL values.

Table 3

Template for deriving a MRL proposal

| Liver | Kidney | Muscle | Skin + fat | Milk | Eggs | Honey | Sum |

TRC [15] (mg kg-1) | | | | | | | —— |

MRC [16] (mg kg-1) | | | | | | | —— |

RMTR [16] | | | | | | | —— |

DITR [17] (mg) | | | | | | | | |

MRL proposed (mg kg-1) | | | | | | | —— |

DITRMRL(mg) | | | | | | | | |

3.2.3.5. Proposal for a withdrawal period

The withdrawal time comprises the period after cessation of the administration of the additive which is necessary to enable the residue levels to fall below the MRLs.

3.3. Studies concerning the safety of use of the additive for users/workers

Workers can be exposed mainly by inhalation or topical exposure while manufacturing or handling or using the additive. For example, farm workers are potentially exposed when handling or mixing the additive. Additional information on how the substances are handled shall be provided.

An assessment of risk to workers shall be included. Where available, experience in the manufacturing plant is often an important source of information in evaluating the risks to workers from exposure to the additive itself by both airborne and topical routes. Of particular concern are additives/additive-treated feeds and/or animal excreta, which are in, or may give rise to, a dry powdery form, and feed additives which may have allergenic potential.

3.3.1. Toxicological risk assessment for user/worker safety

Risks to workers shall be assessed in a series of studies using the additive in the form for which the application has been submitted. Acute inhalation toxicity studies shall be performed unless the product is unlikely to form a respirable dust or mist. Studies on skin irritancy must be performed, and if these give negative results, mucous membrane (e.g. eye) irritancy shall be assessed. Allergenic potential/skin sensitisation potential shall also be assessed. The toxicity data generated to meet consumer safety (see 3.2.2) shall be used to assess the potential systemic toxicity of the additive. All these shall be assessed, if necessary, by direct measurement and specific studies.

3.3.1.1. Effects on the respiratory system

Evidence shall be provided that airborne levels of dust or mist of the additive will not constitute a hazard to the health of users/workers. This evidence shall include, where necessary:

- inhalation tests in laboratory animals;

- published epidemiological data and/or the applicants own data on its work plant and/or irritancy; and

- respiratory system sensitisation tests.

Acute inhalation toxicity studies shall be performed if particles or droplets with a diameter of less than 50 μm constitute more than 1 % on a weight basis of the product.

Protocols for acute inhalation toxicity studies should be in line with OECD Guideline 403. If sub-chronic toxicity studies are considered necessary, they should follow OECD Guidelines 412 (Repeated Dose Inhalation Toxicity: 28-day or 14-day study) or 413 (Sub-chronic Inhalation Toxicity: 90-day study).

3.3.1.2. Effects on the eyes and skin

Where available, direct evidence of absence of irritancy and/or sensitisation shall be provided from known human situations. This shall be supplemented by findings from validated animal tests for skin and eye irritation, and for sensitisation potential using the appropriate additive. Allergic potential — skin sensitisation potential shall also be assessed. Protocols for these studies should be in line with OECD Guidelines 404 (Dermal Irritation/Corrosion), 405 (Eye Irritation/Corrosion), 406 (Skin Sensitisation), 429 (Skin Sensitisation — local lymph-node assay).

If corrosive properties are known, either from published data or specific in vitro tests, then further in vivo tests shall not be performed.

Dermal toxicity must be considered, if the additive is toxic by inhalation. Studies must be in line with OECD Guideline 402 (Acute Dermal Toxicity).

3.3.1.3. Systemic toxicity

The toxicity data generated to meet consumer safety and other requirements (including repeated dose toxicity, mutagenicity, carcinogenicity and reproductive testing and metabolic fate) shall be used to assess systemic toxicity.

3.3.1.4. Exposure assessment

Information shall be provided on how the use of the additive is likely to give rise to exposure by all routes (inhalation, through the skin or by ingestion). This information shall include a quantitative assessment, where available, such as typical airborne concentration, dermal contamination or ingestion. Where quantitative information is not available, sufficient information shall be given to enable an adequate assessment of exposure to be made.

3.3.2. Measures to control exposure

Using the information from the toxicology and exposure assessment, a conclusion shall be drawn about the risks to health of the users/workers (inhalation, irritancy, sensitisation and systemic toxicity). Precautionary measures may be proposed to reduce or eliminate exposure. However, use of personal protective devices shall only be regarded as a measure of last resort to protect against any residual risk once control measures are in place. It is preferable, for example, to consider reformulation of the product.

3.4. Studies concerning the safety of use of the additive for the environment

Consideration of the environmental impact of additives is important since administration of additives typically occurs over long periods, often involves large groups of animals and the active substance(s) may be excreted to a considerable extent either as the parent compound or its metabolites.

To determine the environmental impact of additives, a stepwise approach shall be followed. All additives have to be assessed through Phase I to identify those additives which do not need further testing. For the other additives a second phase (Phase II) assessment is needed to provide additional information, based upon which further studies may be considered necessary. These studies shall be conducted according to Directive 67/548/EEC.

3.4.1. Phase I assessment

The purpose of Phase I assessment is to determine if a significant environmental effect of the additive or its metabolites is likely and whether a Phase II assessment is necessary (see decision tree).

Exemption from Phase II assessment may be made on one of two criteria, unless there is scientifically-based evidence for concern:

(a) the chemical nature and the biological effect of the additive and its conditions of use indicate that impact will be negligible, i.e. where the additive is:

- a physiological or natural substance that will not result in a substantial increase of the concentration in the environment; or

- intended for non-food producing animals;

(b) the worst case Predicted Environmental Concentration (PEC) is too low to be of concern. The PEC shall be evaluated for each compartment of concern (see below), assuming that 100 % of the dose ingested is excreted as the parent compound.

If the applicant cannot demonstrate that the additive falls into one of these exemption categories, a Phase II assessment will be required.

3.4.1.1. Additives for terrestrial animals

When excreta from livestock are applied on land, the use of feed additives can lead to contamination of soil, ground water, and surface water (via drainage and run-off).

The worst case PEC for soil (PECsoil) would arise considering all excreted compounds being spread on land. If the PECsoil (default: 5 cm depth) is less than 10 μg/kg, no further assessment is required.

If the PEC for contamination of groundwater (PECgw) is less than 0,1 μg/l, no Phase II assessment of the environmental impact of the additive on groundwater is necessary.

3.4.1.2. Additives for aquatic animals

Feed additives used in aquaculture can result in contamination of sediment and water. The compartment of concern for the environmental risk assessment for fish farmed in cages is assumed to be the sediment. For fish farmed in land-based systems the effluent flowing to surface water is considered to pose the major environmental risk.

The worst case PEC for sediment (PECsediment) would arise considering all excreted compounds being deposited in the sediment. If the PECsediment (default: 20 cm depth) is less than 10 μg/kg wet weight, then no further assessment is required.

If the PEC in the surface water (PECsw) is less than 0,1 μg/l, no further assessment is required.

Phase I — Decision tree

Is the additive a physiological/natural substance of established safety?

NO

YES

STOP

Is the additive intended for non-food producing animals only?

NO

YES

STOP

FOR ADDITIVES USED IN TERRESTRIAL SPECIES

Has the additive a PEC in ground water ≥ 0,1 µg/l or PEC soil ≥ 10 µg/kg?

FOR ADDITIVES USED IN AQUATIC SPECIES

Has the additive a PEC in surface water ≥ 0,1 µg/l or PEC sediment ≥ 10 µg/kg?

NO

YES

NO

YES

STOP

PHASE II

STOP

PHASE II

+++++ TIFF +++++

3.4.2. Phase II assessment

The aim of Phase II is to assess the potential for additives to affect non-target species in the environment, including both aquatic and terrestrial species or to reach groundwater at unacceptable levels. It is not practical to evaluate the effects of additives on every species in the environment that may be exposed to the additive following its administration to the target species. The taxonomic levels tested are intended to serve as surrogates or indicators for the range of species present in the environment.

The Phase II assessment is based on a risk quotient approach, where the calculated PEC and Predicted No Effect Concentration (PNEC) values for each compartment shall be compared. The PNEC is determined from experimentally determined endpoints divided by an appropriate assessment factor. The PNEC value shall be calculated for each compartment.

The Phase II assessment starts with a refinement of the PEC if possible, and uses a two-tiered approach to the environmental risk assessment.

The first tier, Phase IIA, makes use of a limited number of fate and effect studies to produce a conservative assessment of risk based on exposure and effects in the environmental compartment of concern. If the ratio of the PEC to the PNEC is lower than one (1), no further assessment is required, unless bioaccumulation is expected.

If the PEC/PNEC ratio predicts an unacceptable risk (ratio > 1), the applicant shall progress to Phase IIB to refine the environmental risk assessment.

3.4.2.1. Phase II A

In addition to the compartments considered in Phase I, the PEC for surface water has to be calculated considering runoff and drainage.

Based on data not considered in Phase I, a more refined PEC can be calculated for each environmental compartment of concern. In ascertaining the refined PEC, account shall be taken of:

(a) the concentration of active substance(s)/metabolites of concern in manure/fish faeces following administration of the additive to animals at the proposed dose level. This calculation shall include consideration of dosage rates and amount of excreta produced;

(b) the potential degradation of the excreted active substance(s)/metabolites of concern during normal manure processing practice and storage prior to its application to land;

(c) the adsorption/desorption of the active substance(s)/metabolites of concern onto soil or sediment for aquaculture, preferentially determined by studies in soil/sediment (OECD 106);

(d) degradation in soil and water/sediment systems (OECD 307 and 308, respectively); and

(e) other factors such as hydrolysis, photolysis, evaporation, dilution through ploughing.

The highest value for the PEC obtained from these calculations for each environmental compartment of concern shall be adopted for Phase II risk assessment purposes.

If a high persistence in soil/sediment is anticipated (time to degradation of 90 % of original concentration of the compound: DT90 > 1 year), the potential for accumulation shall be considered.

The concentrations of additives (or metabolites) producing serious adverse effects for various trophic levels in the environmental compartments of concern shall be determined. These tests are mostly acute tests and should follow OECD or similar well-established guidelines. Studies for the terrestrial environment shall include: toxicity to earthworms; three terrestrial plants; and soil micro-organisms (e.g. effects on nitrogen fixation). Studies for the fresh water environment shall include: toxicity to fish; Daphnia magna; algae; and a sediment dwelling organism. In case of sea cages, three species of different taxa of sediment dwelling organisms shall be studied.

Calculation of the PNEC value shall be carried out for each compartment of concern. The PNEC is normally derived from the lowest toxicity value observed in the above tests and dividing by a safety factor of at least 100 depending on the endpoint and number of test species used.

The potential for bioaccumulation can be estimated from the value of the n-octanol/water partition coefficient, Log Kow. Values ≥ 3 indicate that the substance may bioaccumulated. In order to assess the risk for secondary poisoning it shall be considered whether to carry out a bioconcentration factor (BCF) study at Phase IIB.

3.4.2.2. Phase IIB (more detailed ecotoxicological studies)

For those additives where, following Phase IIA assessment, an environmental risk cannot be excluded, more information is required on the effects on biological species in the environmental compartment(s) in which Phase IIA studies indicate possible concern. In this situation, further tests are needed to determine the chronic and more

specific effects on appropriate microbial, plant, and animal species. This additional information will allow the application a lower safety factor.

Suitable additional ecotoxicity tests are described in a number of publications, e.g. in OECD Guidelines. Careful choice of such tests is necessary to ensure that they are appropriate to the situation in which the additive and/or its metabolites may be released and dispersed in the environment. The refinement of the effect assessment for soil (PNECsoil) could be based on studies on the chronic effects on earthworms, additional studies on soil microflora and a number of relevant plant species, studies on grassland invertebrates (including insects) and feral birds.

The refinement of the effect assessment for water/sediment could be based on chronic toxicity tests on the most sensitive aquatic/benthic organisms identified in Phase IIA assessment.

Bioaccumulation studies, if necessary, should be performed according to OECD Guideline 305.

4. SECTION IV: STUDIES CONCERNING THE EFFICACY OF THE ADDITIVE

Studies shall demonstrate the efficacy for each proposed use and satisfy at least one of the characteristics set out in Article 5(3) of Regulation (EC) No 1831/2003, according to the categories and functional groups of feed additives as provided by Article 6 and Annex I of the said Regulation. Moreover such studies must permit the evaluation of the efficacy of the additive according to common farming practices in the EU.

The experimental design used must be justified according to the additive use, animal species and category. When using animals, the trials shall be conducted such that their health and husbandry conditions do not adversely affect the interpretation of the results. The positive and negative effects, both technological and biological, shall be described for each experiment. Absence of effects that impair the distinctive features of animal products shall also be demonstrated. Trials shall ideally be compliant with the criteria established by a recognised, externally-audited, quality assurance scheme. In the absence of such a scheme, evidence shall be provided to show that the work was done by qualified personnel using appropriate facilities and equipment and responsible to a named study director.

The trial protocol shall be carefully drawn up by the study director with regard to general descriptive data, for example methods, apparatus and materials used, details of the species, breed or strain of the animals, their number and the conditions under which they were housed and fed. For all studies involving animals, the experimental conditions shall be described according to 3.1.1.3. Final reports, raw data, study plans and well characterised and identified test substances shall be archived for future reference.

Studies shall be designed to demonstrate the efficacy of the lowest recommended dose of additive by targeting sensitive parameters in comparison to a negative and, optionally, a positive control group. Such studies shall also include the maximum recommended dose, where this is proposed. No single design is recommended, flexibility being provided to allow for scientific discretion in the design and conduct of the studies.

Attention shall also be paid to known or potential biological or chemical interactions between the additive, other additives and/or veterinary medicines and/or components of the diet, where this is relevant to the efficacy of the additive concerned (e.g.

compatibility of microbial additive with coccidiostats and histomonostats or organic acid).

4.1. In vitro studies

For all technological and some sensory additives affecting the characteristics of feed, efficacy shall be demonstrated using a laboratory-based study. The study shall be designed to cover a representative range of materials to which the additive will be applied. Results shall be evaluated preferably by parameter-free tests, and shall demonstrate expected changes with a probability of $P \leq 0,05$.

In vitro studies, particularly those which simulate aspects of the gastrointestinal tract, may be used for other types of additives in order to support the efficacy. These studies should be capable of statistical evaluation.

4.2. Short term efficacy studies with animals

Bioavailability studies may be used to demonstrate the extent to which a novel form or source of a nutrient or colorant can substitute for an equivalent additive already approved or established.

Digestion/balance studies may be used in support of animal performance studies to provide evidence of mode of action. In some cases, particularly in relation to environmental benefits, efficacy may be better demonstrated by balance studies and may be used in preference to long term efficacy studies. Such experiments shall use numbers and species/categories of animals appropriate to the conditions of use proposed.

Other short term efficacy studies with animals may be proposed as appropriate, and these may substitute for long term efficacy studies with animals, provided that this is fully justified.

4.3. Long term efficacy studies with animals

The studies should be carried out at least at two different locations.

The experimental design used must include consideration of adequate statistical power and Type 1 and 2 risks. The protocol must be sufficiently sensitive to detect any effects from the additive at the lowest recommended dose (Type 1 α risk, $P \leq 0,05$ in general and $P \leq 0,1$ for ruminants, minor species, pets and non-food producing animals) and of sufficient statistical power to guarantee that the experimental protocol meets the study objective. The Type 2 β risk shall be lower than or equal to 20 % in general, and 25 % for experiments with ruminants, minor species, pets and non-food producing animals, hence a power $(1-\beta)$ greater than or equal to 80 % (75 % for ruminants, minor species, pets and non food producing animals).

It is recognised that the nature of some additives make it difficult to define experimental conditions under which optimal results may be achieved. Consequently, the possibility of using meta-analysis shall be considered when the number of trials available is greater than three. For this reason, similar protocol designs shall be used for all trials so that data can eventually be tested for homogeneity and pooled (if tests so indicate) for statistical evaluation at a level of $P \leq 0,05$.

4.4. Duration of long term efficacy studies with target animals

Generally, the duration of efficacy trials shall correspond to the application period claimed.

Efficacy trials shall be carried out according to farming practices in European Union and be of the minimum duration as stated by Annex IV.

If an additive is applied for a specific and shorter period than given by the animal category definition, it shall be administered according to the proposed conditions of use. However, the observation period shall not be shorter than 28 days and shall involve the relevant end-points (e.g., for sows for reproduction number of piglets born alive when considering the gestation period, or the number and weight of weaned piglets when considering the lactation period).

For other species or animal categories for which a minimum duration period of studies was not established in Annex IV, a period of administration shall be taken in to account, according to the proposed conditions of use.

4.5. Efficacy requirements for additive categories and functional groups

For all additives intended to have an effect on animals, in vivo studies are requested.

For the categories of zootechnical additives and coccidiostats and histomonostats, efficacy shall be demonstrated by at least three long term efficacy studies. However, for some zootechnical additives and the other additive categories having an effect on animals, short term efficacy studies may be accepted if efficacy can be unequivocally demonstrated.

For other additive categories without a direct effect on animals at least one in vitro efficacy study shall be provided.

4.6. Studies on the quality of animal products where this is not the effect claimed

In order to demonstrate that the additive does not have a negative effect or other effect not requested on the organoleptic and nutritional (hygienic and technological if appropriate) characteristics of food deriving from animals fed with the additive (when this is not the effect desired), appropriate samples shall be taken during one of the efficacy trials. Two groups shall be observed: an unsupplemented group; and a group with the highest dosage proposed for the additive. The data shall allow statistical evaluation. Omission of these studies shall be adequately justified.

5. SECTION V: POST-MARKET MONITORING PLAN

According to Article 7(3)(g) of Regulation (EC) No 1831/2003, a proposal for post-market monitoring shall be submitted for certain categories of additives in order to trace and identify any direct or indirect, immediate, delayed or unforeseen effects resulting from the use of the additive on human or animal health or the environment, in accordance with the characteristics of the products concerned.

The design of the monitoring plan shall be detailed on a case-by-case basis and identify who (e.g. applicant, users) will carry out the various tasks that the monitoring plan requires, who is responsible for ensuring that the monitoring plan is set into place and carried out appropriately, and ensure that there is a route by which the competent control authorities. The Commission and the Authority will be informed of any observed adverse effects, without prejudice to the provisions on supervision laid down in Article 12 of Regulation (EC) No 1831/2003.

In cases where the active substance is also a recognised antibiotic and its use has been shown to select resistant bacterial strains at its feed use level, field studies to monitor for bacterial resistance to the additive shall be undertaken as part of post-market monitoring.

For coccidiostats and histomonostats, field monitoring of Eimeria spp. and Histomonas meleagridis resistance, respectively, shall be undertaken, preferably during the latter part of the period of authorisation.

[1] OJ L 50, 20.2.2004, p. 44.

[2] OJ L 196, 16.8.1967, p. 1. Directive as last amended by Directive 2006/121 of the European Parliament and of the Council (OJ L 396, 30.12.2006, p. 852; corrected by OJ L 136 29.5.2007, p. 281).

[3] OJ L 152, 30.4.2004, p. 1; corrected by OJ L 216, 16.6.2004, p. 3.

[4] OJ L 165, 30.4.2004; corrected by OJ L 191, 28.5.2004, p. 1.

[5] OJ L 117, 8.5.1990, p. 1. Directive as last amended by Commission Decision 2005/174/EC (OJ L 59, 5.3.2005, p. 20).

[6] OJ L 76, 22.3.1991, p. 35. Directive as last amended by Directive 2001/58/EC (OJ L 212, 7.8.2001, p. 24).

[7] OJ L 262, 17.10.2000, p. 21.

[8] OJ L 224, 18.8.1990, p. 1. Regulation as last amended by Commission Regulation (EC) No203/2008 (OJ L 60, 5.3.2008, p. 18).

[9] M. Thompson et al.: Harmonized Guidelines For Single Laboratory Validation Of Methods Of Analysis (IUPAC Technical Report) Pure Appl. Chem., Vol. 74, No. 5, pp. 835-855, 2002.

[10] OJ L 221, 17.8.2002, p. 8. Decision as last amended by Decision 2004/25/EC (OJ L 6, 10.1.2004, p. 38).

[11] A non-exhaustive list is available in: www.efsa.europa.eu/en/science/feedap/feedap_opinion/993.html

[] Muscle and skin in natural proportion.

[] For pig 50 g of fat and skin in natural proportion.

[] fat and skin in natural proportion.

[15] Considering the proposed withdrawal time.

[16] Ideally established at the same time as TRC.

[17] Calculated from TRC values.

ANNEX III

SPECIFIC REQUIREMENTS TO BE SATISFIED BY THE DOSSIER PROVIDED FOR IN ARTICLE 3 WITH RESPECT TO CERTAIN CATEGORIES OF ADDITIVES OR CERTAIN PART ICULAR SITUATIONS, AS PROVIDED FOR IN ARTICLE 7(5) OF REGULATION (EC) No 1831/2003

Regulation (EC) No 1831/2003 foresees additional assistance for the preparation of dossiers, where necessary, for each category of additives or for other particular aims according to Article 7(5) of Regulation (EC) No 1831/2003.

List of the specific requirements for establishing dossiers for:

(1) Technological additives

(2) Sensory additives

(3) Nutritional additives

(4) Zootechnical additives

(5) Coccidiostats and histomonostats

(6) Extrapolation from major to minor species

(7) Pets and other non food-producing animals

(8) Additives already authorised for use in food

(9) Modification of authorisations

(10) Renewal of authorisations

(11) Re-evaluation of certain additives already authorised under Directive 70/524/EEC.

Any applications may be submitted following more than one of the specific requirements listed above.

General conditions

Reasons shall be given for the omission from the dossier of any data prescribed in these sections.

1. TECHNOLOGICAL ADDITIVES

1.1. Section I: summary of the dossier

The whole of the Section I of Annex II applies.

1.2. Section II: identity, characterisation and conditions of use of the additive; methods of analysis

The Section II of Annex II applies as following:

- for additives not subject to a specific holder of the authorisation the paragraphs 2.1.2, 2.1.3, 2.1.4, 2.1.4.2, 2.2, 2.3.1, 2.3.2, 2.4.1, 2.4.2, 2.4.4, 2.5, 2.6 apply;

- for other additives subject to a specific holder of the authorisation, the whole of Section II applies.

1.3. Section III: studies concerning the safety of the additive

Subsections 3.1, 3.2 and 3.4 of Annex II do not apply to silage additives where it can be demonstrated that:

- no detectable amounts of the active substance(s) or relevant metabolites or the active agent(s) survive in the final feed; or

- the active substance(s) and agent(s) occur as normal constituents of silage and use of the additive does not substantially increase their concentration compared to silage prepared without use of the additive (i.e. where there is no substantial change in exposure).

In the other cases the whole of Section 3 of Annex II applies.

1.3.1. Studies concerning the safety of use of the additive to the target animals

For xenobiotic [1] substances: the full subsection 3.1 of Annex II applies.

1.3.1.1. Tolerance studies for the target species

For silage additives:

- the product shall be added to a basal diet and results compared to a negative control with the same diet. The basal diet may contain a single source of silage prepared without the use of an additive.

- the dose selected for the tolerance studies shall be a multiple of the concentration present in the ensiled material at the time of normal use where this can be conclusively established. Particular consideration shall be given to product containing viable micro-organisms and their capacity for survival and multiplication during ensiling.

Tolerance studies can usually be limited to a ruminant species, normally the dairy cows. Studies involving other species are required only when the nature of the ensiled material makes it more appropriate for use with non-ruminants.

Other substances:

for the other substances requesting authorisation as technological additives not already authorised for feed use the absence of harm to animals at the highest proposed level shall be demonstrated. This demonstration may be limited to one experiment in one of the most sensitive target species or in one laboratory animal species.

1.3.1.2. Microbial studies

The whole of subsection 3.1.2 of Annex II applies.

1.3.2. Studies concerning the safety of use of the additive for consumers

1.3.2.1. Metabolic and residue studies

Metabolic and residue studies are not required if:

(1) the substance or its metabolites are not present in the feedingstuff at time of feeding; or

(2) the substance excreted unchanged, or its metabolites can be demonstrated to be essentially not absorbed; or

(3) the substance is absorbed in the form of physiological compounds; or

(4) the active component(s) of the additive consists only of micro-organisms or enzymes).

Metabolic studies also are not required if the substance is naturally present in significant amounts in food or feedingstuffs or the substance is a normal constituent of body fluids or tissues. However, in these cases, there is a requirement for residue studies which can be limited to the comparison of the tissues/products levels in an untreated group and in the group supplemented with the highest recommended dose.

1.3.2.2. Toxicological studies

Toxicological studies are not required if:

(1) the substance or its metabolites are not present in the feedingstuff at time of feeding; or

(2) the substance is absorbed in the form of physiological compound(s); or

(3) the product consists of micro-organisms commonly encountered in ensiled materials or those already used in food; or

(4) the product consists of enzymes with a high degree of purity arising from micro-organisms with a history of documented safe use.

For micro-organisms and enzymes not excluded above, genotoxicity studies (including mutagenicity) and a subchronic oral toxicity study are required. Genotoxicity studies shall not be made in the presence of living cells.

For xenobiotic substances, not exempted above, the whole of subsection 3.2.2 Annex II applies.

For other substances a case by case approach shall be taken, taking into account the level and means of exposure.

1.3.2.3. Assessment of consumer safety

The whole of subsection 3.2.3 of Annex II applies for additives requested for food producing animals.

1.3.3. Studies concerning the safety of use of the additive for users/workers

The whole of subsection 3.3 of Annex II applies. Additives containing enzymes and micro-organisms are assumed to be respiratory sensitisers unless convincing evidence to the contrary is provided.

1.3.4. Studies concerning the safety of use of the additive for the environment

The whole of subsection 3.4 of Annex II applies. For silage additives, the effects of the additive on the production of effluent from clamp or silo during ensiling shall be considered.

1.4. Section IV: studies concerning the efficacy of the additive

Technological additives are intended to improve or stabilise the characteristics of feed but have generally no direct biological effect on animal production. Evidence of the efficacy of the additive must be provided by means of appropriate criteria as reflected in recognised acceptable methods, under the intended practical conditions of use in comparison with appropriate control feed.

Efficacy will be assessed by in vitro studies, with the exception of substances for control of radionuclide contamination. The appropriate end-points are indicated in the following table for the various functional groups.

End-points for different technological additives

Functional group | End-points for demonstration of efficacy |

(a)Preservatives | Inhibition of microbial growth, particularly that of biotic and spoilage organisms. The period for which a preserving effect is claimed shall be demonstrated. |

(b)Antioxidants | Protection against oxidative damage of key nutrients/components during feedingstuff processing and/or storage. The period for which a protecting effect is claimed shall be demonstrated. |

(c)Emulsifiers | Formation/maintenance of stable emulsions of otherwise immiscible or poorly miscible feed ingredients. |

(d)Stabilisers | Maintenance of the physico-chemical state of feedingstuffs. |

(e)Thickeners | Viscosity of the feed materials or feedingstuffs. |

(f)Gelling agents | Formation of a gel resulting in a change in the texture of the feedingstuff. |

(g)Binders | Pellet durability or performance of pellet formation. |

(h)Substances for control of radionuclides | Evidence of reduced contamination of food of animal origin. |

(i)Anti-caking agents | Flow ability. The period for which an anti-caking effect is claimed shall be demonstrated. |

(j)Acidity regulators | pH and/or buffering capacity in feedingstuffs. |

(k)Silage additives | Improved production of silage;Inhibition of undesirable micro-organisms;Reduction of effluents;Improved aerobic stability. |

(l)Denaturants | Indelible identification of feed materials. |

Silage additives

Separate tests shall be made to demonstrate the effect requested on ensiling process [2]. The trials shall be performed with one example of each of the following categories (where all or unspecified forages are involved):

- easy to ensile forage: > 3 % soluble carbohydrates in fresh material (e.g. whole plant maize, ryegrass, brome grass or sugar beet pulp),

- moderately difficult to ensile forage: 1,5—3,0 % soluble carbohydrates in the fresh material (e.g. meadow grass, fescue or wilted alfalfa);

- difficult to ensile forage: < 1,5 % soluble carbohydrates in the fresh material (e.g., orchard grass or leguminous plants).

Where requests are restricted to sub-categories of forage described in terms of dry matter (DM), the dry matter range shall be explicitly stated. Three tests shall then be made with material representative of the range, where possible using examples of different botanical origin.

Specific tests are required for the particular feedingstuffs.

The duration of the study normally shall be 90 days or longer at a constant temperature (recommended range 15—25 oC). Use of a shorter duration must be justified.

As a rule measurements of the following parameters shall be provided in comparison to the negative control:

- dry matter and calculated dry matter losses (corrected for volatiles),

- pH- decrease,

- concentration of volatile fatty acids (e.g. acetic, butyric and propionic acids) and lactic acid,

- concentration of alcohols (ethanol),

- concentration of ammonia (g/kg of total nitrogen), and

- content of hydro-soluble carbohydrates.

In addition, other microbiological and chemical parameters shall be included as appropriate to substantiate the specific claim made (e.g. numbers of lactate assimilating yeasts, numbers of Clostridia, numbers of Listeria and biogenic amines).

An effect sought for effluent reduction will be judged against the total volume of effluent produced over the entire experimental period, taking into account the likely effect on the environment (e.g. ecotoxicity of the effluent or biological oxygen demand). Reduction of effluent production shall be demonstrated directly. The capacity of the silo shall be sufficient to allow effluent to be released with the application of pressure. The duration of the study shall normally be 50 days. If a different period is used, this shall be justified.

Improved aerobic stability shall be demonstrated in comparison with a negative control. Stability studies shall be of at least seven days duration after exposure to air and additive shall provide evidence of stability for at least two days longer than that shown by untreated control. It is recommended that the experiment is made at an ambient temperature of 20 oC and a rise in temperature of 3 oC or more above background taken as indicative of instability. Temperature measures may be replaced by measurement of CO2 production.

1.5. Section V: post-market monitoring plan

This section shall apply under provision of Article 7(3)(g) of Regulation (EC) No 1831/2003. That is, a post-market monitoring plan is required only for additives that are GMOs or are produced from GMOs.

2. SENSORY ADDITIVES

2.1. Colourants

2.1.1. Section I: summary of the dossier

The whole of Section I of Annex II applies.

2.1.2. Section II: identity, characterisation and conditions of use of the additive; methods of analysis

The Section II of Annex II applies as following:

- for additives not subject to a specific holder of the authorisation the paragraphs 2.1.2, 2.1.3, 2.1.4, 2.1.4.2, 2.2, 2.3.1, 2.3.2, 2.4.1, 2.4.2, 2.4.4, 2.5, 2.6 apply;

- for other additives subject to a specific holder of the authorisation, the whole of Section II applies.

2.1.3. Section III: studies concerning the safety of the use of the additive

Subsection 3.3 of Annex II applies fully for every additive.

(1) For substances which, when fed to animals, add colours to food of animal origin Section III subsections 3.1, 3.2 and 3.4 of Annex II apply in full.

(2) For substances that add or restore colour in feedingstuffs, studies concerning Section III subsection 3.1 shall be performed on animals receiving the additive at the recommended dose. Evidence can also be provided by reference to existing scientific literature. Section III subsections 3.2 and 3.4 of Annex II apply.

(3) For substances which favourably affect the colour of ornamental fish or birds, studies concerning Section III subsection 3.1 of Annex II are required and shall be performed on animals receiving the additive at the recommended dose. Evidence can also be provided by reference to existing scientific literature. However, subsections 3.2 and 3.4 are not required.

2.1.4. Section IV: studies concerning the efficacy of the additive

The whole of Section IV of Annex II applies.

(a) For substances which, when fed to animals, add colour to food of animal origin:

changes of the colour of products obtained from animals receiving the additive at the recommended conditions of use shall be measured using the appropriate methodology. It shall be demonstrated that the use of the additive does not adversely affect product stability or organoleptic and nutritional qualities of the food. In principle, if effects of a particular substance on the composition/characteristics of animal products are well documented, then other studies (e.g. bioavailability studies) may provide adequate evidence of efficacy.

(b) For substances that add or restore colour in feedingstuffs:

evidence of efficacy shall be provided by adequate laboratory studies reflecting the intended conditions of use in comparison with control feedingstuffs.

(c) For substances which favourably affect the colour of ornamental fish and birds:

studies demonstrating the effect(s) shall be performed on animals receiving the additive at the recommended levels of use. Colour changes shall be measured using the appropriate methodology. Evidence of efficacy may also be provided by other experimental studies (e.g. bioavailability) or by reference to scientific literature.

2.1.5. Section V: post-market monitoring plan

This section shall apply under the provision of Article 7(3)(g) of Regulation (EC) No 1831/2003. That is, a post-market monitoring plan is required only for additives that are GMOs or are produced from GMOs.

2.2. Flavouring compounds

2.2.1. Section I: summary of the dossier

The whole of Section I of Annex II applies.

2.2.2. Section II: identity, characterisation and conditions of use of the additive; methods of analysis

In general, in the case of the group "natural products", whole plants, animals and other organisms and parts of these or products thereof resulting from very limited processing such as crushing, grinding or drying (e.g. many herbs and spices), shall not be considered as falling under this functional group flavourings of the category sensory additives.

For the purposes of the evaluation of applications of these products, flavourings are classified as follows:

1. Natural products:

1.1. Natural products — botanically defined.

1.2. Natural products — non-plant origin.

2. Natural or corresponding synthetic chemically defined flavourings

3. Artificial substances.

The relevant group, to which the product object of the application belongs, shall be indicated. In case the product does not fit into any of the above groups, this shall be mentioned and justified.

2.2.2.1. Characterisation of active substance(s)/agent(s)

The whole of the subsection 2.2 of Annex II applies.

In addition:

For all groups of flavourings, the relevant identification number(s) (such as FLAVIS [3], Council of Europe [4], JECFA, CAS [5] or any other internationally accepted numbering system) used specifically for the identification of flavouring products in feed and food shall always be provided when available.

(1) Natural products — botanically defined

The characterisation of the natural botanically defined products shall include the scientific name of the plant of origin, its botanical classification (family, genus, species, if appropriate subspecies and variety) and the common names and synonyms in as many European languages as possible or other language(s) (such as the one(s) of the place(s) of cultivation or origin) where available. The parts of the plant used (leaves, flowers, seeds, fruits, tubers, etc) and for lesser known plants the place of cultivation, identification criteria, and other relevant aspects of these plants shall be indicated. The major components of the extract shall be identified and quantified and its range or variability provided. Special attention shall be given to impurities as mentioned in subsection 2.1.4 of Annex II. The concentrations of substances of toxicological concern [6] for humans or animals which may occur in the plant from which the extract is produced shall also be reported.

The pharmacological or related properties of the plant of origin, its parts or of derived products thereof shall be fully investigated and reported.

(2) Natural products — non plant origin

An equivalent approach to the above may be used.

(3) Natural or corresponding synthetic chemically defined flavourings

Besides the general requirements of subsection 2.2.1.1 of Annex II, the origin of the flavouring shall be specified.

2.2.2.2. Method of production and manufacture

The whole of the subsection 2.3 of Annex II applies.

In the case of non chemically well defined natural products, usually complex mixtures of many compounds obtained by an extraction process, a detailed description of the extraction process shall be provided. It is recommended to use in the description the relevant terminology such as essential oil, absolute, tincture, extract and related terms [7] widely used for botanically defined flavouring products to describe the extraction process. The extraction solvents used shall be specified, the precautions taken to avoid residues of the solvents, and the levels of residues where these are of toxicological concern if their presence would be unavoidable. The terms used to characterise the extract may include a reference to the method of extraction.

2.2.2.3. Methods of analysis

(1) For natural products (either botanically defined or non-plant origin) which do not contain substances of toxicological concern for humans or animals, the standard requirement for methods of analysis of subsection 2.6 of Annex II may be replaced by a simpler qualitative method of analysis fit for the purpose for major or characteristic components of the product.

(2) For natural or corresponding synthetic chemically defined flavourings which are not substances of toxicological concern for humans or animals the standard requirement for methods of analysis of subsection 2.6. of Annex II may be replaced by a simpler qualitative method of analysis fit for the purpose.

The whole of subsection 2.6 of Annex II applies for all other flavourings, such as those natural extracts which contain substances of toxicological concern, natural or corresponding synthetic chemically defined flavourings which are substances of toxicological concern themselves and artificial flavourings.

2.2.3. Section III: studies concerning the safety of the additive

For all flavourings, animal exposure and intake calculations both from natural exposure and following addition of the flavouring to feedingstuffs shall be provided.

For flavouring belonging to the group artificial substances, the whole of Section III of Annex II applies.

2.2.3.1. Studies concerning the safety of use of the additive for target animals

(1) Natural products (either botanically defined or non–plant origin)

The safety of these products may be assessed on the basis of its major and characteristic components and also considering known substances of toxicological concern. If the major or characteristic components are not already authorised as chemically defined flavourings or as feed additives, then it has to be verified whether they are substances of toxicological concern for humans or animals, and its toxicological properties have to be provided in accordance with subsection 3.1 of Annex II.

(2) Natural or corresponding synthetic chemically defined flavourings

If these substances are authorised flavourings for humans, the safety for target species may be assessed taking into account the comparison between the level of intake by the target species from feed proposed by the applicant with that by humans from food. Metabolism and toxicological data on which the assessment for human used was made shall be submitted.

In all other cases different from the case where both levels of intake are similar, such as where the level of intake by the target animal proposed be the applicant is substantially higher than that by human from food or where the substance is not authorised in food, the safety for the target animals may be assessed by taking into account the following data: the principle of threshold of toxicological concern [8], available toxicological and metabolism data for related compounds, and chemical structural alert consideration (following by analogy of the Commission Regulation (EC) No 1565/2000 of 18 July 2000 laying down the measures necessary for the adoption of an evaluation program in application of Regulation (EC) No 2232/96 of the European Parliament and of the Council) [9].

Tolerance studies are needed only where threshold values are exceeded or cannot be determined.

2.2.3.2. Studies concerning the safety of use of the additive for consumers

Evidence that the metabolites of the flavouring do not result in an accumulation in the animal of products of toxicological concern for humans shall be provided. In the case that the use of the requested flavouring product as a consequence of its addition to feedingstuffs results in residues in food of animal origin, detailed calculation of consumer exposure shall be provided.

(a) Metabolic and residue studies

(1) Natural products (either botanically defined or non–plant origin)

The safety of these products for humans when used as flavourings in feed, as regards its metabolism, may be based on the metabolism (in the target animal) and residues studies of their major and characteristic components and the absence of substances of toxicological concern in the extract.

If the major or characteristic components are not already authorised as chemically defined flavourings or if the level of intake by the target animals from feed is substantially higher than that by humans from food, the whole of subsection 3.2.1 of Annex II is required.

(2) Natural or corresponding synthetic chemically defined flavourings

If these products are not authorised as flavourings for humans or if the level of intake by the target animal from feed as proposed be the applicant is substantially higher than that by human from food, available data on metabolic fate shall be provided and used to assess the potential accumulation in edible tissues and products according to subsection 3.2.1 of Annex II.

(b) Toxicological studies

(1) Natural products (either botanically defined or non–plant origin)

The safety of these products for humans when used as flavouring in feed may be based on the toxicological data of their major or characteristic components and the absence of substances of toxicological concern in the extract.

A toxicological package is required when the metabolic studies of the major or characteristic compounds show that there is accumulation in animal tissues or

products and the threshold of toxicological concern for the target animal is exceeded. This toxicological package shall comprise genotoxicity studies, including mutagenicity and a subchronic oral toxicity study, according to subsection 3.2.2 of Annex II.

(2) Natural or corresponding synthetic chemically defined flavourings

A toxicological package comprising genotoxicity studies, including mutagenicity and a subchronic oral toxicity study, according to subsection 3.2.2 of Annex II, is required when the metabolic studies of these products show that there is accumulation in animal tissues or products and the threshold of toxicological concern for the target animal is exceeded.

2.2.3.3. Studies concerning the safety of use of the additive for users/workers

The whole of subsection 3.3 of Annex II applies.

2.2.3.4. Studies concerning the safety of use of the additive for the environment

The whole of subsection 3.4 of Annex II applies.

2.2.4. Section IV: studies concerning the efficacy of the additive

Evidence of the flavouring properties, usually on the basis of the published literature, shall be provided. This may also be demonstrated by experience of practical use, where available, otherwise animal studies may be required.

It has to be fully investigated and reported if the product object of the application exerts other functions in the feed, animal or food of animal origin besides the one in the definition of flavouring compounds in Annex I of Regulation (EC) No 1831/2003.

2.2.5. Section V: post-market monitoring plan

This section shall apply under provision of Article 7(3)(g) of Regulation (EC) No 1831/2003. That is, a post-market monitoring plan is required only for additives that are GMOs or are produced from GMOs.

3. NUTRITIONAL ADDITIVES

3.1. Section I: summary of the dossier

The whole of Section I of Annex II applies.

3.2. Section II: identity, characterisation and conditions of use of the additive; methods of analysis

The Section II of Annex II applies as following:

- for additives not subject to a specific holder of the authorisation the paragraphs 2.1.2, 2.1.3, 2.1.4, 2.1.4.2, 2.2, 2.3.1, 2.3.2, 2.4.1, 2.4.2, 2.4.4, 2.5, 2.6 apply;

- for other additives subject to a specific holder of the authorisation, the whole of Section II applies.

3.3. Section III: studies concerning the safety of the additives

3.3.1. Studies concerning the safety of use of the additive for the target species

3.3.1.1. Tolerance of the target species

1. No studies are required for urea, and amino acids, their salts and analogues authorised by Directive 82/471/EEC and compounds of trace elements and vitamins, pro-vitamins and chemically well-defined substances having similar effect which do not have a potential to accumulate already authorised as feed additives under Directive 70/524/EEC.

2. For those additives that fall within the functional group "vitamins, pro-vitamins and chemically well-defined substances having similar effect" and having a potential to

accumulate, tolerance will only be required to be demonstrated for compounds for which potency is expected or has been demonstrated to be different from that of the well established vitamin(s). In certain cases elements of the tolerance test (design or criteria) could be combined with one of the efficacy trials.

3. Tolerance will be demonstrated for urea derivatives amino acid analogues and compounds of trace elements not previously authorised. The fermentation products will be requested by tolerance demonstration, unless the active substance is separated from the crude fermentation product and highly purified, or the production organism has a history of apparent safe use and well known about its biology to exclude a potential for the production of toxic metabolites.

4. Where the application is for all animal species/categories, one tolerance study on the most sensitive species (or even an appropriate laboratory animal) under the most recent knowledge is sufficient.

3.3.1.2. Microbial studies

The whole of subsection 3.1.2 of Annex II applies.

3.3.2. Studies concerning the safety of use of the additive for consumers

3.3.2.1. Metabolic and residue studies

Metabolic studies normally are not required. For urea derivatives, ruminal metabolism shall be studied in the efficacy trials.

Residue or deposition studies are only required for those additives that fall within the functional group "vitamins, pro-vitamins and chemically well-defined substances, having similar effect" that have a potential for accumulation in the body and for the functional group of compounds of trace elements where bioavailability has been enhanced. In that case, the procedure described in subsection 3.2.1 of Annex II does not apply. The requirement is limited to the comparison of the levels in the tissues or products between the group supplemented with the highest dose of the substance claimed and a positive control (reference compound).

3.3.2.2. Toxicological studies

These are required for fermentation products and additives not already authorised. For fermentation products, genotoxicity and subchronic toxicity studies must be provided unless:

1. the active substance is separated from the crude fermentation product and is highly purified; or

2. the production organism has a history of apparent safe use and there is sufficient knowledge of its biology to exclude a potential for the production of toxic metabolites.

Where the production organism belongs to a group in which some strains are known to produce toxins, their presence shall be specifically excluded.

3.3.2.3. Assessment of consumer safety

The whole of subsection 3.2.3 of Annex II applies.

3.3.3. Studies concerning the safety of use of the additive for users/workers

The whole of subsection 3.3 of Annex II applies

3.3.4. Studies concerning the safety of use of the additive for the environment

The whole of subsection 3.4 of Annex II applies for new active substances belong to the compound of trace elements.

3.4. Section IV: studies concerning the efficacy of the additive

Efficacy studies are not required for urea, amino acids, amino acid salts and analogues already authorised as feed additives, compounds of trace elements already authorised as feed additives and vitamins, pro-vitamins and chemically well-defined substances having similar effect already authorised as feed additives.

A short term study is required to support efficacy for urea derivatives, amino acid salts and analogues not already authorised as feed additives, compounds of trace elements not already authorised as feed additives and for vitamins, pro-vitamins and chemically well-defined substances having similar effect not already authorised as feed additives.

For other substances for which a nutritional effect is requested at least one long term efficacy study under provisions of Section 4 of Annex II is requested.

Where required, studies shall demonstrate that the additive can provide the animals' nutritional requirements. Tests shall include a test group with a diet that contains the nutrient at concentrations below the animals' requirements. However, trials using a severely deficient control group shall be avoided. Generally, it will be sufficient to demonstrate efficacy in a single animal species or category including laboratory animals.

3.5. Section V: post-market monitoring plan

This section shall apply under provision of Article 7(3)(g) of Regulation (EC) No 1831/2003.

4. ZOOTECHNICAL ADDITIVES

4.1. Zootechnical additives other than enzymes and micro-organisms

4.1.1. Section I: summary of the dossier.

The whole of Section I of Annex II applies.

4.1.2. Section II: identity, characterisation and conditions of use of the additive; methods of analysis

The whole of Section II of Annex II applies.

4.1.3. Section III: studies concerning the safety of the additives

4.1.3.1. Studies concerning the safety of use of the additive for target animals

The whole of subsection 3.1 of Annex II applies.

4.1.3.2. Studies concerning the safety of use of the additive for consumer

(1) Metabolic and residue studies

These studies are not required if:

- the substance or its metabolites can be demonstrated to be excreted unchanged and essentially to be not absorbed; or

- the substance is absorbed in physiological form and physiological level of compound(s).

No metabolic studies are needed if the substance is naturally present in significant amounts in food or feedingstuffs or if the substance is a normal constituent of body fluids or tissues. However, in these cases, there is a requirement for residue studies which can be limited to a comparison of the levels in the tissues or products in an untreated group to the levels found in the group supplemented with the highest recommended dose.

In all other cases the whole of subsection 3.2.1 of Annex II applies.

(2) Toxicological studies

Toxicological studies are not required if the substance is absorbed in the form of physiological compound(s).

For xenobiotic substances the whole of subsection 3.2.2 of Annex II applies.

For other substances, a case by case approach shall be used, taking into account the level and means of exposure, and any omission of data prescribed in this section must be fully justified.

(3) Assessment of consumer safety

The whole of subsection 3.2.3 of Annex II applies for food producing animals.

4.1.3.3. Studies concerning the safety of the additive for users/workers

The whole of subsection 3.3 of Annex II applies.

4.1.3.4. Studies concerning the safety of the additive for the environment

The whole of subsection 3.4 of Annex II applies

4.1.4. Section IV: studies concerning the efficacy of the additive

The whole of Section IV of Annex II applies.

(1) Additives favourably affecting animal production, performance or welfare and for the functional group "other zootechnical additives".

The effects can only be demonstrated in relation to each target animal species or category. Depending on the properties of the additive, outcome measures may be based either on performance characteristics (e.g. feed efficiency, average daily gain, increasing of animal products), carcass composition, herd performance, reproduction parameters or animal welfare. Evidence of the mode of action can be provided by short term efficacy studies or laboratory studies measuring relevant end-point.

(2) Additives favourably affecting the environmental consequences of animal production

For these additives which favourably affect the environment (e.g. reduced nitrogen or phosphorus excretion or reduced methane production, off-flavours), evidence of efficacy for the target species can be given by three short term efficacy studies with animals showing significant beneficial effects. The studies shall take into consideration the possibility of an adaptive response to the additive.

4.1.5. Section V: post-market monitoring plan

This section shall apply under provision of Article 7(3)(g) of Regulation (EC) No 1831/2003.

4.2. Zootechnical additives: enzymes and micro-organisms

4.2.1. Section I: summary of the dossier

The whole of Section I of Annex II applies.

4.2.2. Section II: identity, characterisation and conditions of use of the additive; methods of analysis

The whole of Section II of Annex II applies.

4.2.3. Section III: studies concerning the safety of the additives

4.2.3.1. Studies concerning the safety of use of the additive for the target animals

The whole of subsection 3.1.1 of Annex II applies.

Applicants are encouraged to use, wherever possible, at least a 100-fold overdose in the experimental group and consequently reduce the number of end-points required. A

concentrated form of the additive can be used for this purpose. Concentration shall be adjusted by reducing the amount of carrier present but the ratio of active agent(s)/substance(s) to the other fermentation products must remain the same as in the final product. For enzymes, the diet shall provide the appropriate substrate(s).

The whole of subsection 3.1.2 of Annex II applies for all micro-organisms and for those enzymes with a direct catalytic effect on elements of the microbiota or which otherwise are claimed to affect the gut microbiota.

Where there is novel exposure or a substantial increase in the extent of exposure to micro-organisms, additional studies may be necessary to demonstrate the absence of adverse effects on the commensal microbiota of the digestive tract. For ruminants, direct counts of the microbiota will be necessary only if indicted by evidence of an adverse change to rumen function (measured in vitro as a change in volatile fatty acid concentrations, reduction in propionate concentration or reduced cellulolysis).

4.2.3.2. Studies concerning the safety of the additive use for consumer

(1) Metabolic and residue studies are not required.

(2) Toxicological studies, according to subsection 3.2.2 of Annex II.

Enzymes and micro-organisms form only a part of the whole additive which, in most cases, can include other components originated from the fermentation process. Consequently, it is necessary to test the additive to ensure it does not contain mutagenic or otherwise materials that can harm human consumers of food derived from animals feed with feedingstuffs or water treated with these additives.

However, most viable bacteria intended for direct or indirect ingestion by mammals (including humans) are selected from groups of organisms with a history of apparent safe use or from groups where the toxic hazards are well defined. Similarly, the hazards associated with micro-organisms currently used for the production of enzymes generally are well recognised and substantially reduced by modern production methods. Therefore, for enzymes from microbial sources and for micro-organisms with a history of apparent safe use and where the components of fermentation process are well defined and know, toxicity tests (e.g. oral toxicity or genotoxicity testing) are not considered necessary. However, for both live organisms and those used for the production of enzymes, the specific concerns in section 2.2.2.2 of Annex II shall always be addressed.

When the organism or its application is novel and insufficient is known about the biology of the (production) organism to exclude a potential for the production of toxic metabolites, genotoxicity and oral toxicity studies made with additives containing viable micro-organisms or enzymes shall be introduced. In this case, they shall take the form of genotoxicity studies including mutagenicity and a subchronic oral toxicity study. It is recommended that such studies are performed with the cell-free fermentation broth or in the case of a solid state fermentation, an appropriate extract.

4.2.3.3. Studies concerning the safety of the additive for users/workers

The whole of subsection 3.3 of Annex II applies except:

- enzymes and micro-organisms, as proteinaceous substances, are assumed to be respiratory sensitisers unless convincing evidence to the contrary is provided. Therefore, no direct testing is required.

- the formulation of the product (e.g. micro-encapsulation) may obviate the need for some or all tests. In such cases, appropriate justification shall be provided.

4.2.3.4. Studies concerning the safety of the additive for the environment

The whole of subsection 3.4 of Annex II fully applies for micro-organisms which are not of gut origin or are not ubiquitous in the environment.

4.2.4. Section IV: studies concerning the efficacy of the additives

The whole of Section IV of Annex II applies.

(1) Additives favourably affecting animal production, performance or welfare and for the functional group "other zootechnical additives".

The effects can only be demonstrated in relation to each target animal species or category. Depending on the properties of the additive, outcome measures may be based either on performance characteristics (e.g. feed efficiency, average daily gain, increasing of animal products), carcass composition, herd performance, reproduction parameters or animal welfare. Evidence of the mode of action can be provided by short term efficacy studies or laboratory studies measuring relevant end-point.

(2) Additives favourably affecting the environmental consequences of animal production.

For these additives which favourably affect the environment (e.g. reduced nitrogen or phosphorus excretion or reduced methane production, off-flavours), evidence of efficacy for the target species can be given by three short term efficacy studies with animals showing significant beneficial effects. The studies shall take into consideration the possibility of an adaptive response to the additive.

4.2.5. Section V: post-market monitoring plan

This section shall apply under provision of Article 7(3)(g) of Regulation (EC) No 1831/2003.

5. COCCIDIOSTATS AND HISTOMONOSTATS

5.1. Section I: summary of the dossier

The whole of Section I of Annex II applies

5.2. Section II: identity, characterisation and conditions of use of the additive; methods of analysis

The whole of Section II of Annex II applies

5.3. Section III: studies concerning the safety of the additives

5.3.1. Studies concerning the safety of use of the additive for target animals

The whole of the subsection 3.1 of Annex II applies

5.3.2. Studies concerning the safety of use of the additive for consumer

The whole of the subsection 3.2 of Annex II applies

5.3.3. Studies concerning the safety of use of the additive for users/workers

The whole of the subsection 3.3 of Annex II applies

5.3.4. Studies concerning the safety of use of the additive for environment

The whole of the subsection 3.4 of Annex II applies

5.4. Section IV: studies concerning the efficacy of the additive

These additives protect the animals from the results of an invasion of Eimeria spp. or Histomonas meleagridis. Importance shall be attached to evidence of the specific effects of the additive (e.g. species controlled) and its prophylactic properties (e.g. reduction in morbidity, mortality, oocyst count and lesion score). Information on the

effect on growth and feed conversion (fattening birds, replacement layers and rabbits), effects on hatchability (breeding birds) shall be provided, as appropriate.

The required efficacy data shall derive from three types of target animal experiments:

- artificial single and mixed infections

- natural/artificial infection to simulate use conditions

- actual use conditions in field trials

Experiments with artificial single and mixed infections (e.g. battery cages for poultry) are intended to demonstrate the relative effectiveness against the parasites and do not require replication. Three significant results are required for studies simulating use conditions (e.g. floor pen studies with poultry, battery cage studies with rabbits). Three field studies in which a degree of natural infection is present are also required.

5.5. Section V: post-market monitoring plan

This section of Annex II shall apply under provision of Article 7(3)(g) of Regulation (EC) No 1831/2003.

6. EXTRAPOLATION FROM MAJOR TO MINOR SPECIES

Minor species are defined in Article 1(2) of this Regulation.

A more limited submission will normally be accepted for a proposed extension of the authorised use to a species which is physiologically comparable to one in which the use of the additive has already been granted.

The following requirements apply only to requested authorisations for minor species of additives already authorised for major species. For requested authorisations for new feed additives requested only for minor species, all sections fully apply, depending on the category/functional group of the additive (see corresponding specific requirements of Annex III).

6.1. Section I: summary of the dossier

The whole of Section I of Annex II applies.

6.2. Section II: identity, characterisation and conditions of use of the additive; methods of analysis

The Section II of Annex II applies as following:

- for additives subject to a specific holder of the authorisation, the whole of Section II applies,

- for other additives the paragraphs 2.1.2, 2.1.3, 2.1.4, 2.1.4.2, 2.2, 2.3.1, 2.3.2, 2.4.1, 2.4.2, 2.4.4, 2.5, 2.6 apply.

6.3. Section III: studies concerning the safety of the use of the additive

6.3.1. Studies concerning the safety of use of the additive for the target animals

6.3.1.1. Tolerance of the target species

The requirements for the different categories/functional groups of additives apply.

In principle, tolerance studies for minor species are not required if the additive showed a wide margin of safety (at least a factor of 10) in the relevant physiologically similar major species.

If three major target species (including monogastric and ruminant mammals and poultry) showed a similar and wide margin of safety, no additional tolerance studies would be required for non-physiologically similar minor species (e.g. horses or rabbits). Where tolerance is required, the duration of the studies for minor species

(except rabbits) shall be at least 28 days for growing animals and 42 days for adult animals. For rabbits, the following durations apply: rabbits for fattening: 28 days; breeding does: one cycle (from insemination to the end of the weaning period). If rabbits suckling and weaned are applied for, a period of 49 days (beginning one week after birth) would be considered sufficient and must include the does until weaning. For fish (other than salmonidae) a 90-day period is required.

6.3.2. Studies concerning the safety of use of the additive for the human consumers

6.3.2.1. Metabolic studies

The requirements for the different categories and functional groups of additives apply.

In addition, metabolic studies are not required if the additive is already authorised for use in a species which is physiologically comparable to the minor species for which the authorisation is sought. In the absence of physiological similarity, a comparison of metabolic profile based on in vitro studies (e.g. performed in hepatocytes using labelled compound) is considered sufficient to assess metabolic proximity.

If the minor species is not physiologically similar to a major species, then an indication of the metabolic fate of the additive shall be obtained in the minor species.

6.3.2.2. Residue studies

Only marker residue quantification in edible tissues and products is needed when metabolic proximity is given or demonstrated. In all other cases, subsection 3.2.1.2 of Annex II fully applies.

6.3.2.3. Assessment of consumer safety

Proposal for Maximum Residue Limits (MRLs)

Setting of MRLs can be done by assuming that no significant differences in the content of residues occur in the edible tissues of minor species compared to a similar major species.

MRLs can be extrapolated within classes of animals as follows:

- from major growing ruminants to all growing ruminants;
- from milk of dairy cows to milk of other dairy ruminants;
- from pigs to all monogastric mammals, excluding horses;
- from chickens or turkeys to other poultry;
- from laying hens to other laying birds; and
- from Salmonidae to all fin fish.

MRLs for horses could be extrapolated when MRLs for a major ruminant and a major monogastric mammal exist.

If identical MRLs were derived in cattle (or sheep), pigs and chicken (or poultry), which represent major species with different metabolic capacities and tissue composition, the same MRLs can also be set for ovine, equidae and rabbits, which means an extrapolation is considered possible to all food-producing animals except fish. Considering the Committee for Medicinal Products for Veterinary Use (CVMP) guideline [10] on the establishment of MRLs for Salmonidae and other finfish, which already allows an extrapolation from MRLs in muscle of a major species to Salmonidae and other finfish provided that the parent substances is acceptable as marker residue for the MRL in muscle and skin, MRLs can be extrapolated to all-food-producing animals.

Analytical methods shall be available for monitoring residues in edible tissue and products of all food-producing animals.

6.3.3. Studies concerning the safety of use of the additive for users/workers

The whole of subsection 3.3 of Annex II applies.

6.3.4. Studies concerning the safety of use of the additive for the environment

Environmental risk assessment can be extrapolated from the assessment performed for the physiologically comparable major species. For additives intended to be used in rabbits, the whole section applies taking into consideration the requirements for each category/functional group of additives.

6.4. Section IV: studies concerning the efficacy of the additive

Where the additive is already approved for a physiologically comparable major species for the same function and where the mode of action of the additive is known or demonstrated, evidence of the same mode of action in the minor species can be taken as evidence of efficacy. Where no such link can be made, efficacy shall be demonstrated following the general rules for Section IV in Annex II. In some cases it may be appropriate to combine animal species in the same productive stage (e.g. goats and sheep used for milk production). Significance should be demonstrated in each study ($P \leq 0,1$) or, if possible, by meta-analysis ($P \leq 0,05$).

If efficacy demonstration is required, the duration of efficacy studies shall be analogous to the comparable production stages of the physiologically comparable major species. In other cases, the minimum study duration shall follow the relevant provisions in subsection 4.4 of Annex II and Annex IV.

6.5. Section V: post-market monitoring plan

This section of Annex II shall apply under provision of Article 7(3) (g) of Regulation (EC) No 1831/2003.

7. PETS AND OTHER NON FOOD-PRODUCING ANIMALS

Pets and other non food-producing animals are defined in Article 1(1) of this Regulation.

7.1. Section I: summary of the dossier

The whole of Section I of Annex II applies.

7.2. Section II: identity, characterisation and conditions of use of the additive; methods of analysis

The Section II of Annex II applies as following:

- for additives subject to a specific holder of the authorisation, the while of Section II applies

- for other additives the paragraphs 2.1.2, 2.1.3, 2.1.4, 2.1.4.2, 2.2, 2.3.1, 2.3.2., 2.4.1, 2.4.2, 2.4.4, 2.5, 2.6 apply.

7.3. Section III: studies concerning the safety of the additive

7.3.1. Studies concerning the safety of use of the additive for the target animals

The requirements for the different categories/functional groups of additives apply. Where a tolerance study is required, its duration shall be at least 28 days.

A tolerance study is not required if the additive has shown a comparable and wide margin of safety in three major species (including monogastric and ruminant mammals and poultry).

7.3.2. Studies concerning the safety of use of the additive for consumers

This subsection is not usually required. Consideration shall be given to the safety of the owner.

7.3.3. Studies concerning the safety of use of the additive for users/workers

The whole of subsection 3.3 of Annex II applies.

7.3.4. Studies concerning the safety of use of the additive for the environment

Subsection 3.4 of Annex II is not required.

7.4. Section IV: studies concerning the efficacy of the additive

The requirements for the different categories/functional group of additives apply.

When the additive, for which animal studies are required, has been previously authorised for other physiological similar species, no further demonstration of efficacy is required provided the requested effect and mode of action are the same. If the additive has not been previously authorised, the requested effect, or the mode of action are different than former authorisation, efficacy shall be demonstrated following the general rules for Section IV in Annex II.

The duration of the long term efficacy trials shall be at least 28 days.

7.5. Section V: post-market monitoring plan

This section of Annex II shall apply under provision of Article 7(3) (g) of Regulation (EC) No 1831/2003.

8. ADDITIVES ALREADY AUTHORISED FOR USE IN FOOD

8.1. Section I: summary of the dossier

The whole of Section I of Annex II applies.

8.2. Section II: identity, characterisation and conditions of use of the additive; methods of analysis

The Section II of Annex II applies as following:

- for additives subject to a specific holder of the authorisation, the whole of Section II applies,

- for other additives the paragraphs 2.1.2, 2.1.3, 2.1.4, 2.1.4.2, 2.2, 2.3.1, 2.3.2., 2.4.1, 2.4.2, 2.4.4, 2.5, 2.6 apply.

8.3. Section III: studies concerning the safety of the additives

The most recent formal assessments of the safety of the food additive shall be included and shall be supplemented with any subsequently produced data.

For those additives which are authorised as food additives or approved as components for foodstuffs in the European Union without any restriction, studies concerning the safety for the consumer and the workers are generally not necessary.

Subsections 3.1, 3.2 and 3.3 of Annex II shall be provided considering the present knowledge on the safety of these substances when used in food. Accordingly, such substances also used in food can be classified as:

- ADI not specified (without an explicit indication of the upper limit of intake, assigned to substances of very low toxicity),

- ADI or UL established, or

- no ADI allocated (applicable to substances for which the available information is not sufficient to establish their safety).

8.3.1. Studies concerning the safety of use of the additive for the target animals

If the use level as for the feed additive is similar to that used in food, the safety for target species can be assessed based on the in vivo toxicological data available, a consideration of chemical structure and the metabolic capacity of the target species. If the use level in feed is considerably higher than the corresponding use in food, a tolerance study in the target animal may be required, depending on the nature of the substance.

8.3.2. Studies concerning the safety of use of the additive for consumers

If the use as a feed additive results in a higher consumer exposure, or to a different pattern of metabolites than that resulting from use in food, then further toxicological and residue data will be required.

8.3.2.1. Food additives for which an ADI is not specified

Assessment of the safety for consumers is not required, except when the use of the additive in feed leads to a different pattern of metabolites than when used in food.

8.3.2.2. Food additives with an established ADI or UL

Consumer safety must be assessed taking into consideration the additional exposure from feed use, or specific exposure related to metabolites arising from the target species. This can be done by extrapolating residue data from literature.

Where residue studies are necessary, the requirement is limited to a comparison of the tissue or product levels in an untreated group to the group supplemented with the highest dose that is claimed.

8.3.2.3. Food additives for which no ADI is allocated

The reasons why an ADI was not allocated shall be clearly specified. If concerns arise from this, and the use of the additive in feed would contribute to a significant increase in consumer exposure, a full toxicological evaluation is required.

Additional exposure from feed use can be extrapolated from residue data from the literature.

Where residue studies are necessary, the requirement is limited to a comparison of the levels in tissues or products in an untreated group with the group supplemented with the highest dose that is claimed.

8.3.3. Studies concerning the safety of use of the additive for users/workers

The whole of the subsection 3.3 of Annex II applies.

Precautionary measures set for handling these substances used in food shall be taken into account when considering user safety for the feed additive.

8.3.4. Studies concerning the safety of use of the additive for the environment

Subsection 3.4 of Annex II is required.

8.4. Section IV: studies concerning the efficacy of the additive

Where the function requested for feed is the same as that used in food, no further demonstration of efficacy might be necessary. Otherwise the requirements for efficacy are as those shown in Section IV of Annex II.

8.5. Section V: post-market monitoring plan

This section of Annex II shall apply under provision of Article 7(3)(g) of Regulation (EC) No 1831/2003.

9. MODIFICATION OF THE AUTHORISATIONS

Since reliance can be placed on the evaluation of the data supplied for previous authorisations, a dossier prepared for an application under Article 13(3) of Regulation (EC) No 1831/2003 needs to comply only with the requirements listed below.

An application for modification of the terms included in an existing authorisation Regulation, such as the identification, the characterisation or the conditions of use of the additive, shall demonstrate that the modification does not have any harmful effect on the target species, the consumer, the user or the environment. An additive can be considered as identical for this purpose if the active substance(s) or agent(s) and the conditions of use are the same, its purity is essentially similar and no new components of concern have been introduced. For such products an abridged application may be submitted as it will normally not be necessary to repeat studies to demonstrate the safety for the target species, the consumer and the environment and efficacy.

The application shall address the following requirements:

1. the whole of Annex I applies — this includes details of the modification requested;

2. the whole of Section II of Annex II applies;

3. data must be provided indicating that the, chemical or biological characteristics of the additive are essentially the same to those of the established product;

4. where appropriate, evidence for bioequivalence shall be provided either by specification, or by published literature or from specific studies. Where bioequivalence is not fully demonstrated, conformity of the withdrawal period with the MRL has to be demonstrated;

5. evidence shall be presented that in the light of current scientific knowledge that the additive remains safe under the approved conditions for target species, consumers, workers and the environment;

6. a report on the results of the post-market monitoring, if such monitoring requirements are included in the authorisation, shall be provided; and

7. the specific data supporting the request for change must be submitted in compliance with the relevant parts of Sections III, IV and V of Annex II.

10. RENEWAL OF AUTHORISATIONS

Applications for renewal of authorisation under Article 14 of Regulation (EC) No.1831/2003 shall comply with the following requirements:

10.1. Section I: summary of the dossier

The whole of Section I of Annex II applies. A copy of the original Community authorisation for placing the feed additive on the market, or the last renewal of authorisation, shall be provided. An updated dossier shall be prepared according to the most up-to-date requirements and a list providing all variations since the original authorisation, or the last renewal of authorisation shall be submitted. The applicant has to provide a summary of the dossier, detailing the scope of the application, and any new information that has become available since the previous authorisation/renewal in terms of identity and safety.

10.2. Section II: identity, characterisation and conditions of use of the additive; methods of analysis

The Section II of Annex II applies as following:

- for additives subject to a specific holder of the authorisation, the whole of the Section II applies,

- for other additives the paragraphs 2.1.2, 2.1.3, 2.1.4, 2.1.4.2, 2.2, 2.3.1, 2.3.2, 2.4.1, 2.4.2, 2.4.4, 2.5, 2.6 apply.

Evidence shall be presented to show that the additive has not been significantly changed or altered in composition, purity or activity in respect of the additive that was authorised. Any change in the manufacturing process shall be reported.

10.3. Section III: studies concerning the safety of the additives

Evidence shall be presented that in the light of the current knowledge the additive remains safe under the approved conditions for target species, consumers, workers and the environment. A safety update for the period since the original authorisation, or the last renewal of authorisation with information on the following items shall be presented:

- reports on adverse effects including accidents (previously unknown effects, severe effects of any type, increased incidence of known effects) for target animals, consumers, users and the environment. The report on adverse effects shall include the nature of the effect, number of affected individuals/organisms, outcome, conditions of use, and causality assessment,

- reports on previously unknown interactions and cross-contaminations,

- data from residue monitoring, where appropriate,

- data from epidemiologic and/or toxicological studies,

- any other information concerning the safety of the additive and risks of the additive to animals, humans, and environment.

If no further information is provided on any of these issues, the reasons for this shall be clearly identified.

A report on the results of the post-market monitoring program shall be provided, if such a monitoring requirement is included in the previous authorisation.

Where, as provided for in Article 14(2)(d) of Regulation (EC) No 1831/2003, the application for renewal of the authorisation includes a proposal for amending or supplementing the conditions of the original authorisation, inter alia, the conditions concerning future monitoring, the specific data supporting the proposal for amendment must be submitted in compliance with the relevant parts of Sections III, IV and V of Annex II.

11. RE-EVALUATION OF CERTAIN ADDITIVES ALREADY AUTHORISED UNDER DIRECTIVE 70/524/EEC

The additives concerned by this point 11 are additives which were authorised under Directive 70/524/EEC and are to be re-evaluated in accordance with Article 10(2) of Regulation (EC) No 1831/2003 and which belong to the following groups:

- antioxidant substances,

- flavouring and appetising substances,

- emulsifying and stabilising substances, thickeners and gelling agents,

- colourants, including pigments,

- preservatives,

- vitamins, provitamins and chemically well-defined substances having similar effect,

- trace elements,

- binder, anti-caking agents and coagulants,

- acidity regulators, and

- radionuclide binders.

The level and quality of risk evaluation for these additives shall be similar to other additives. However, due to their long history of safe use, data from studies already published may be used, under provisions provided by this Regulation, to show that the additive remains safe under the approved conditions for the target species, consumers, users and the environment.

11.1. Section I: summary of the dossier

The whole of Section I of Annex II applies.

11.2. Section II: identity, characterisation and conditions of use of the additive; methods of analysis

The Section II of Annex II applies as following:

- for additives not subject to a specific holder of the authorisation the paragraphs 2.1.2, 2.1.3, 2.1.4, 2.1.4.2, 2.2, 2.3.1, 2.3.2, 2.4.1, 2.4.2, 2.4.4, 2.5, 2.6 apply;

- for other additives subject to a specific holder of the authorisation, the whole of Section II applies.

11.3. Section III: studies concerning the safety of the additives

Where an additive has been assessed for safety for target species, consumers, users/workers and the environment, a summary of the safety studies submitted for the previous authorisation, plus any new information arising since the previous authorisation shall be provided. Where a formal safety assessment has not been undertaken for the use of the substance as a feed additive, studies and data from the scientific literature can be used provided it is equivalent to that which would be required in a new application. Otherwise, a complete set of safety studies shall be provided.

11.4. Section IV: studies concerning the efficacy of the additive

Where appropriate, the compliance with the requirement of efficacy provided for in Article 5(3) of Regulation (EC) No 1831/2003 may be demonstrated by submission of material other than studies, in particular relating to the long history of use.

11.5. Section V: post-market monitoring plan

This section of Annex II shall apply under provision of Article 7(3) (g) of Regulation (EC) No 1831/2003.

[1] A xenobiotic is a chemical substance which is not a natural component of the organism exposed to it. It can also cover substances which are present in much higher concentrations than are usual.

[2] For purpose of this Regulation, "ensiling process" means process by which natural deterioration of organic matter is controlled by acidification in anaerobic condition resulting from natural fermentation or/and addition of silage additives.

[3] Identification number for chemically defined flavouring substances used in FLAVIS, the EU Flavour Information System, the database used within the Commission Regulation (EC) No 1565/2000 of 18 July 2000 (OJ L 180, 19.7.2000 p. 8) laying down the measures necessary for the adoption of an evaluation programme in application of Regulation (EC) No 2232/96 of the European Parliament and of the Council (OJ L 299, 23.11.1996, p. 1).

[4] CoE no.: Council of Europe number used for botanically defined flavouring products in the Council of Europe's Report no. 1 on "Natural sources of flavourings", Volume I, Strasbourg, 2000 and its subsequent volumes.

[5] CAS Number (CAS No) Chemical Abstracts Service Registry Number, unique identifier for chemical substances widely used in chemical inventory listings.

[6] For the purpose of this section of this Regulation, "substance of toxicological concern" means a substance with a tolerable daily or weekly intake (TDI or TWI), an ADI, or with a restriction in its use, or an active principle as defined in Council Directive 88/388/EEC relating to flavourings for use in foodstuffs and to source materials for their production, or an undesirable substance.

[7] Defined in Appendix 4 of the Council of Europe's Report no. 1 on "Natural sources of flavourings", Volume I, Strasbourg, 2000.

[8] JECFA (FAO/WHO, 1996, Food additive series 35, IPCS, WHO Geneva) corresponding threshold for target animal should be adjusted to take into account of animal weight and feed intake.

[9] OJ L 180, 19.7.2000, p. 8.

[10] Note for guidance of the establishment of maximum residue limits for Salmonidae and other fin fish. The European Agency for the Evaluation of Medicinal Products. Veterinary Medicines Evaluation Unit. EMEA/CVMP/153b/97-FINAL.

ANNEX IV

Categories and definitions of target animals and indication of the minimum duration of efficacy studies

1. Table. Animal categories: Pigs

Category | Definition of the animal category | Approximate duration period (weight/age) | Minimum duration of long term efficacy studies |

Period/age | Age | Weight |

Piglets (suckling) | Young porcine animals getting milk from sows | From birth | Up to 21-42 days | Up to 6-11 kg | 14 days |

Piglets (weaned) | Young porcine animals having completed the suckling period and being reared for reproduction or meat production | From 21-42 days | Up to 120 days | Up to 35 kg | 42 days |

Piglets (suckling and weaned piglets) | Young porcine animal from birth being reared for reproduction or meat production purposes | From birth | Up to 120 days | Up to 35 kg | 58 days |

Pigs for fattening | Porcine animals having completed the weaning period and intended for meat production until day of transport to slaughterhouse | From 60-120 days | Up to 120-250 days (or according to local custom) | 80-150 kg (or according to local custom) | Until slaughter weight, but not less than 70 days |

Sows for reproduction | Female porcine animals having been inseminated/mated at least once | From first insemination | | | From insemination to the end of the second weaning period (two cycles) |

Sows, in order to have benefit in piglets | Female porcine animals having been inseminated/mated at least once | | | | At least two weeks before the parturition until the end of weaning period |

2. Table. Animal categories: Poultry

Category | Definition of the animal category | Approximate duration period (weight/age) | Minimum duration of long term studies for efficacy |

Period | Age | Weight |

Chickens for fattening | Birds raised for fattening | From hatching | Up to 35 days | Up to ~1600 g(up to 2 kg) | 35 days |

Chickens reared for laying | Female birds being reared for consumer egg production or for breeding purposes | From hatching | Up to ~16 weeks (up to 20 weeks) | — | 112 days (if the efficacy data are not available for chickens for fattening) |

Laying hens | Productive female birds held for egg production purposes | From 16-21 weeks | Up to ~13 months (up to 18 months) | From 1200 g (white) 1400 g (brown) | 168 days |

Turkeys for fattening | Birds raised for fattening | From hatching | Up to ~14 weeks (up to 20 weeks) Up to ~16 weeks (up to 24 weeks) | Hens: up to ~7000 g (up to 10000 g) Cocks: up to ~12000 g (up to 20000 g) | 84 days |

Turkeys for breeding purposes | Female and male birds held for breeding purposes | Whole period | From 30 weeks up to ~ 60 weeks | Hens: from ~15000 g Cocks: from ~30000 g | At least six months |

Turkeys reared for breeding | Young female and male birds reared for breeding purposes | From hatching | Up to 30 weeks | Hens: up to ~15000 g Cocks: up to ~30000 g | Whole period (if the efficacy data are not available for turkeys for fattening) |

3. Table. Animal categories: Bovines (domestic bovine animals including bubalus and bison species)

Category | Definition of the animal category | Approximate duration period (weight/age) | Minimum duration of long term studies for efficacy |

Period | Age | Weight |

Calves for rearing | Calves which are reared for reproduction or for beef production | From birth | Up to 4 months | Up to 60-80 kg up to 145 kg) | 56 days |

Calves for fattening | Calves for veal production | From birth | Up to 6 months | Up to 180 kg (up to 250 kg) | Until slaughter but not less than 84 days |

Cattle for fattening | Bovine animals that have completed the weaning period and are destined for meat production until day of transport to slaughterhouse | From full development of rumination | Up to 10-36 months | Up to 350-700 kg | 168 days |

Dairy cows for milk production | Female bovine animals that have produced at least one calf. | | | | 84 days (total lactation period shall be reported) |

Cows for reproduction | Female bovine animals that have been inseminated/mated at least once | From first insemination to the end of second weaning period | | | Two cycles (if the reproduction parameters are requested) |

4. Table. Animal categories: Sheep

Category | Definition of the animal category | Approximate duration period (weight/age) | Minimum duration of long term studies for efficacy |

Period | Age | Weight |

Lambs for rearing | Lambs reared for future reproduction | From birth | Up to 3 months | 15-20 kg | 56 days |

Lambs for fattening | Lambs that are reared for lamb meat production. | From birth | Up to 6 months (or older) | up to 55 kg | Until slaughter weight but not less than 56 days |

Dairy sheep (for milk production) | Sheep that have produced at least one lamb | | | | 84 days (total lactation period shall be reported) |

Ewes for reproduction | Female sheep that have been inseminated/mated at least once | From first insemination to the end of second weaning period | | | Two cycles (if the reproduction parameters are requested) |

5. Table. Animal categories: Goats

Category | Definition of the animal category | Approximate duration period (weight/age) | Minimum duration of long term studies for efficacy |

Period | Age | Weight |

Kids for rearing | Young goats reared for future reproduction | From birth | Up to 3 months | 15-20 kg | At least 56 |

Kids for fattening | Young goats that are reared for goat meat production | From birth | Up to 6 months | | At least 56 days |

Dairy goats (for milk production) | Goats that have produced at least one kid | | | | 84 days (total lactation period shall be reported) |

Goats for reproduction | Female goats that have been inseminated/mated at least once | From first insemination to the end of second weaning period | | | Two cycles (if the reproduction parameters are requested) |

6. Table. Animal categories: Fish

Category | Definition of the animal category | Approximate duration period (weight/age) | Minimum duration of long term studies for efficacy |

Period | Age | Weight |

Salmon and trout | | | | 200-300 g | 90 days or until initial body weight is doubled. |

Salmon and trout | Brood stock | As close to the spawning period as possible | | | 90 days |

7. Table. Animal categories: Rabbits

Category | Definition of the animal category | Approximate duration period (weight/age) | Minimum duration of long term studies for efficacy |

Period | Age | Weight |

Rabbits suckling and weaned | | Beginning one week after birth | | | 56 days |

Rabbits for fattening | Rabbits that are reared for meat production | After weaning period | Up to 8-11 weeks | | 42 days |

Breeding does (for reproduction) | Does, that have been inseminated/mated at least once | From the insemination to the end of the second weaning period | | | Two cycles (if the reproduction parameters are requested). |

Breeding does (in order to have benefits to young rabbits) | Does, that have been inseminated at least once | From first insemination | | | At least 2 weeks before parturition until the end of the weaning period (e.g. for micro-organism product) |

8. Table. Animal Categories: horses

Category | Definition of the animal category | Approximate duration period (weight/age) | Minimum duration of long term studies for efficacy |

Period	Age	Weight
Horses	All categories				56 days