

Guidance for the preparation of dossiers for the re-evaluation of certain additives already authorised under Directive 70/524/EEC

Prepared by the Panel on Additives and Products or Substances used in Animal Feed

(Question No EFSA-Q-2008-410)

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The additives concerned 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](#).

They belong to the following groups:

- antioxidant substances;
- emulsifying and stabilising substances, thickeners and gelling agents;
- preservatives;
- binder, anti-caking agents and coagulants;
- acidity regulators;
- radionuclide binders.

- colourants, including pigments;
- flavouring and appetizing substances.

- vitamins, provitamins and chemically well-defined substances having similar effect;
- trace elements.

This guidance document does not apply to additives containing or produced from GMOs.

The stringency of the risk evaluation for these additives will be no less than that applied to a novel authorisation of a feed additive. However, due to their history of use, data from studies already published may be used, under provisions provided by [Regulation \(EC\) No 429/2008](#), to show that the additive remains safe under the approved conditions for the target species, consumers, users and the environment, provided that a common identity can be established.

THE TECHNICAL DOSSIER – GENERAL ASPECTS

The dossiers must enable an assessment of the additives to be made 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 substance itself, the target animals and the conditions of use. The applicant should refer to the [Regulation \(EC\) No 429/2008](#) in order to evaluate which studies and information should be submitted with the application.

Reasons must be given for the omission from the dossier of any data prescribed there.

The dossier should include detailed reports of all the studies performed, presented in accordance with the numbering system proposed in [Regulation \(EC\) No 429/2008](#). The dossier should 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 should be sufficient. Data from studies that have been conducted and published previously or coming from peer review should 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, should 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 or International Organization for Standardization (ISO).

Where *in vivo* or *in vitro* studies are carried out outside the Community, the applicant should 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, as last amended by Commission [Directive 2004/73/EC](#), or with updated methods recognised by international scientific bodies. The use of methods other than these must be justified.

The studies involving animals should respect the rules on animal welfare laid down by European Community legislation, and they should not be repeated if not necessary. 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 should be encouraged. Such methods should 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 should be in conformity with the rules of Good Laboratory Practice as laid down in [Directive 2004/10/EC](#) and/or EN ISO/IEC 17025:2005. These methods should comply with the requirements laid down in Article 11 of [Regulation \(EC\) No 882/2004](#) 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.

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

Each dossier should 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](#).

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 should submit a summary indicating the main features of the additive concerned. The summary should not contain any confidential information and should 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 should be provided in all cases. When a dossier is submitted by a group of applicants, the name of each of them should be indicated.
- b) identification of the additive

The identification of the additive should contain a summary of the information required according to Annex II and III of [Regulation \(EC\) No 429/2008](#), 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 should 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 Annex II and III of [Regulation \(EC\) No 429/2008](#) should be described. If appropriate, on the basis of the information submitted, the procedure of the method(s) to be used for the analysis for the official controls of the additive or its metabolites in food of animal origin should 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 should 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 of [Regulation \(EC\) No 429/2008](#) should be indicated in the summary.
- e) proposed conditions for use

The proposal for conditions of use should be provided by the applicant(s). In particular the applicant should 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 should be described.
- f) proposal for post-market monitoring

This part should only apply to nutritional additives.

1.2 Scientific summary of the dossier

A scientific summary including details of each part of the documents submitted to support the application should be submitted. This summary should include the conclusions made by the applicant(s).

The summary must follow the order of Annex II of [Regulation \(EC\) No 429/2008](#) 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 should be added.

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

The list should 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 studies reported in the dossier should ideally be based on the actual additive for which re-evaluation is sought. If older studies involving different formulations are presented they must at least allow conclusions to be drawn about the current additive.

In-house identifiers should be avoided unless embedded in third-party documents. In this case a statement is required to confirm that the identifier(s) refers to the formulation(s) for which the claim is made.

2.1. Identity of the additive

2.1.1. Name of the additive

The name of the additive (characterisation of the active substance(s) as defined in the subsection 2.2.1) should be given. Reference to a trade name can be made.

2.1.2 Proposal for classification

A proposal for the classification of the additive in one or more categories and functional groups according to its main functions under Article 6 and Annex I of [Regulation \(EC\) No 1831/2003](#) should be made. Applicants should note that the groups mentioned in the introduction do not in all cases correspond to the functional groups specified under Regulation (EC) No 1831/2003.

Any data from other known uses of the identical active substances (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 and properly referenced.

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

The active substance(s) and all other components of the additive should be listed, giving the proportion by weight in the final product. Evidence should be provided by the analysis of at least five production batches that the amount and nature of the active substance(s) in the additive specified by the applicant is satisfied in practice.

If the active component of the additive is a mixture of active substances, each of which is clearly definable (qualitatively and quantitatively), the active substance(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 should be characterised by constituent(s) contributing to its activity and/or typical major constituent(s).

Without prejudice to any request for supplementary information made by the EFSA 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 scope of [Regulation \(EC\) No 1829/2003](#).

2.1.4 Purity

The applicant should 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. Any substances produced via fermentation should be free of antimicrobial activities relevant to the use of antibiotics in humans or animals. In addition the absence of production organisms in the additive should be confirmed.

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.

Monitoring for contaminants and impurities should be consistent with existing legislation (e.g., [Directive 2002/32/EC](#), or specifications from [European Community food additive authorisations](#)) and recommendations from internationally recognised sources when these are available (e.g., Joint FAO/WHO Expert Committee on Food Additives (JECFA) specifications; [Commission recommendation on the presence of deoxynivalenol, zearalenone, ochratoxin A, T-2 and HT-2 and fumonisins in products intended for animal feeding](#)). Additional measures should be introduced following the HACCP analysis of the specific process, as necessary.

As a guide the following should be considered as minimum requirements:

- for fermentation/cultivation products: microbiological contamination (*Salmonella*, enterobacteriaceae, *E. coli*), mycotoxins,¹ heavy metals (Pb, Hg, Cd) and arsenic. The extent to which spent growth medium is incorporated into the final product should also be indicated. For fermentation products produced by genetically modified micro-organisms, identification and quantification of recombinant DNA in the final product should be provided.
- for plant derived substances: microbiological and botanical contamination (e.g. castor oil plant, weed seeds, rye ergot in particular), mycotoxins, dioxins (PCDD/F) and dioxin-like PCBs, pesticides,² 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 arsenic and maximum values for solvents, where appropriate;
- for mineral substances: heavy metals and arsenic, dioxins (PCDD/F) and dioxin-like 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 should be identified and their concentrations given.

2.1.5 Physical state of each form of the product

Not mandatory, but EFSA recommends the provision of particle size distribution/dusting potential for solid preparations and specific weight for liquid preparations. Studies on particle size distribution should take into consideration particles of inhalable ($\leq 100 \mu\text{m}$) and respirable ($\leq 10 \mu\text{m}$) size.

2.2. Characterisation of the active substance(s)

2.2.1. Description

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

Chemically well-defined substances should be described by generic name, chemical name according to the International Union of Pure and Applied Chemistry ([IUPAC](#)) nomenclature, other generic international names and abbreviations and/or Chemical Abstract Service ([CAS](#)) Number. The structural and molecular formula and molecular weight must be included. Where relevant, data on isomeric forms and accompanying structurally related compounds should be included.

For additives of plant origin the information required under section 2.2.2.1 of the [guidance for sensory additives/flavouring compounds](#) should be provided. The constituent(s) contributing

¹ The selection of mycotoxins for analysis should be made according to the different matrices, where appropriate.

² Residues specified under the undesirable substances directive (Directive 2002/32/EC) and any other pesticide residues of potential concern to target animals and/or consumer safety.

to the claimed effects should be identified. The phytochemical marker(s) characteristic of the plant of origin 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 should be characterised by constituent(s) contributing to its activity and/or typical major constituent(s). A marker compound should be selected which will allow the additive to be identified in the different studies.

The microbial origin of chemical substances produced by fermentation/cultivation should be described and any history of modification should be indicated. The name and taxonomic classification of each micro-organism should be provided, according to the latest published information in the International Codes of Nomenclature (ICN). Microbial strains should 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 should 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 should be described.

2.2.2. Relevant properties

Description of physical and chemical properties should be given. Dissociation constant, pKa, electrostatic properties, melting point, boiling point, density, vapour pressure, solubility in water and in organic solvents, K_{ow} and K_d/K_{oc} , mass spectrometry and absorption spectra, NMR data and any other relevant physical properties should be provided where appropriate.

Micro-organisms used as production strains should not be capable of producing antibiotic substances of use in human and veterinary medicine (see [technical guidance on microbial studies](#)).

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 or additive a description of the manufacturing process should be given. Attention should be drawn to any major changes in the production process which have occurred during the use of the product as a feed additive. A material safety data sheet of chemicals used in the production process should be provided.

2.3.1 Active substance(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) of the additive should be submitted, if appropriate by way of a flowchart. The composition of the fermentation/cultivation media should be provided. Purification methods should be thoroughly described.

2.3.2. Additive

A detailed description of the manufacturing process of the additive should be submitted. The key stages in the preparation of the additive including the point(s) of introduction of the active substance(s) and other components, and any subsequent process 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

A statement of the shelf life of the product and, as appropriate, its stability in premixtures and feed, as currently advised should be provided. Any restrictions on feed processing conditions

should be included. The experimental studies which form the basis for this advice should be summarised.

All stability data should be based on the current system of production/formulation and should satisfy the quality standards as outlined below. If these are not available, then new studies would be required.

Stability is generally measured by the analytical follow-up of the active substance(s) or effects (e.g., pellet durability). For the majority of technological additives, if stability studies in feedingstuffs are considered necessary, stability should be demonstrated by the maintenance of the effect. If specific effects are claimed for a particular form of the additive the stability of that specific form of the additive should be followed. For some chemical mixtures/extracts stability may be assessed by monitoring the concentration of one or more appropriate marker substances. Data should be provided from at least three batches that include at least one observation at the beginning and one at the end of the storage period.

Where there is a loss of stability, measured by the analytical follow-up of the active substance, potential degradation or decomposition products should be characterised, where appropriate.

Stability studies are not required for inorganic compounds of trace elements.

2.4.1.1 Shelf life of the additive

The stability on exposure to defined environmental conditions (light, temperature, pH, moisture, oxygen and packing material, as appropriate) should be studied for each formulation of the additive.

The expected shelf-life of the additive as marketed should be proposed, based on at least two model situations covering the likely range of use conditions (e.g., for a solid formulation 25°C, 60% relative air humidity (RH) and 40°C, 75% RH).

Stability studies to determine the shelf-life are normally not required for mineral based products generally assumed to be stable.

2.4.1.2 Stability of the additive used in premixtures and feedingstuffs

The stability of each formulation of the additive at the recommended inclusion level normally should be studied in feedingstuffs manufactured and stored under common conditions, and if relevant, in premixtures. The quantitative and qualitative composition of the premixtures or the feedingstuffs used for the studies should be given.

Stability studies in feedingstuffs and premixtures should be of at least three and six months' duration, respectively.

2.4.2 Homogeneity

A statement that the current product can be homogeneously distributed into premixtures and feedingstuffs, as appropriate, should be provided. The experimental studies which form the basis for this statement should be summarised.

Homogeneity data should be based on the current system of production/formulation and should satisfy the quality standards as outlined below. If these are not available, then new studies would be required.

The capacity for homogeneous distribution of the feed additive in premixtures and feedingstuffs must be demonstrated, as appropriate. The same criteria as described under 2.4.1 should be used. As a guide, a minimum of ten sub-samples from a single batch (of the premixture or feedingstuff) should be analysed and the coefficient of variation calculated. If homogeneity is demonstrated in the final feedingstuff, there is no need to demonstrate homogeneity of mixing at any preceding stages in feed production (including premixtures).

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 reported.

2.5. Conditions of use of the additive

2.5.1 Mode of use in animal nutrition

The use in feed materials, and where appropriate in compound feedingstuffs, should be described. It should be indicated whether the treated feed is intended for all animal species/categories or whether a restricted list applies. In the later case they should accord with the categories listed in Annex IV of [Regulation \(EC\) No 429/2008](#). Possible contra-indications should be mentioned.

Details of the method of administration and level of inclusion must be provided for premixtures or feedingstuffs, as appropriate. In addition, the proposed doses (minimum and maximum) in the final feedingstuff and the proposed duration of administration must be provided, where appropriate. If a particular use in complementary feedingstuffs for some animal species or categories is intended, the dose should be proposed and justified.

2.5.2. Information related to worker safety

2.5.2.1. Chemical substances

A copy of the material safety data sheet formatted in accordance with the requirements of Commission [Directive 91/155/EEC](#) as amended by [Directive 2001/58/EC](#) should be provided. If necessary, existing measures for the prevention of occupational risks and means of protection during manufacture, handling, use and disposal should be described. Any proposed changes should be justified.

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 should be indicated.

2.6. Methods of analysis and reference samples

Methods of analysis to determine the active substance in the additive itself and in premixtures and feedingstuffs as appropriate should be submitted. These should be suitable for the official control of the feed additive. If there are residues of concern, a method of analysis of the active substance and/or its metabolites (including the marker residue) in the relevant tissues/products should be provided.

These methods will be evaluated by the Community Reference Laboratory (CRL). Details of the requirements specified in the [Regulation \(EC\) No 429/2008](#) A. Applicants should refer to the [guidance provided by the CRL](#).

Methods to determine the identity and the characteristics of the additive (composition of the additive, impurities, physical and chemical properties) should be internationally recognised or otherwise fully described.

3 SECTION III: STUDIES CONCERNING THE SAFETY OF THE ADDITIVE

The studies included in this section are intended to permit assessment of the safety of the use of the additive under the conditions proposed by the applicant for the target species, the consumer, the user/worker and the environment.

The elements required for the safety assessment are described in the EFSA guidance documents for the categories of [technological](#), [sensory](#) and [nutritional additives](#).

Where an additive has already been assessed by a European scientific body following the legislation in force in the Community for safety for target species, consumers, users/workers and the environment, a summary of the safety studies submitted for the previous authorisation in the EU and the scientific opinion on which the authorisation is based must be provided. Moreover, any information related to the safety of the product arising since the previous authorisation must be provided. Special attention should be paid to data which may lead to setting a maximum content of the feed additive in feedingstuffs.

For additives already authorised for use in food see the [technical guidance for additives already authorised for use in food](#).

Where a formal safety assessment has not been undertaken for the use of the substance as a feed additive, a full safety assessment is, in principle, required following the applicable guidelines. However, recognising that such additives have a (long) history of use, some elements of the safety assessment (particularly target species and user safety) may be satisfied by other means (e.g., pre-existing data, publications preferably peer-reviewed).

As a tool to provide information on the safety of the feed additive under the conditions of authorisation, systematic database searches may be used. Relevant scientific databases (including agricultural/aquacultural and medical/veterinary databases) should be searched in a structured manner. The databases examined, search terms used, total and relevant hit rate and any restrictions used should be stated. The database search should cover at least the last 20 years. Copies of the relevant papers should be provided. In order to place the results of database searches into context, where possible, information on use of the generic product (e.g., volume, geographical distribution and time) should be provided.

4 SECTION IV: STUDIES CONCERNING THE EFFICACY OF THE ADDITIVE

The elements required for the assessment of efficacy are described in the EFSA guidance documents for the categories of [technological](#), [sensory](#) and [nutritional additives](#).

Where appropriate, efficacy may be demonstrated by submission of studies, peer-reviewed publications (preferably recent) and/or material other than studies (e.g., the scientific opinion on which the previous authorisation was based).

Evidence of use of the additive in animal nutrition (e.g., volume, geographical distribution and time) could be helpful in assessing the efficacy of the additive.

5 SECTION V: POST-MARKET MONITORING PLAN

A post-market monitoring plan should be proposed for nutritional additives.

This is required 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 product concerned.

The design of the monitoring plan should 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.

It would generally be sufficient to follow the requirements of the Feed Hygiene Regulation ([Regulation \(EC\) No 1831/2003](#)) and Good Manufacturing Practices. The post-market monitoring plan should in all cases ensure that there is a route by which the competent control authorities, the Commission and the EFSA are informed of any observed adverse effects.