GUIDANCE

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Guidance on the renewal of the authorisation of feed additives

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Abstract

This guidance document is intended to assist the applicant in the preparation and the presentation of an application, as foreseen in Article 7.6 of Regulation (EC) No 1831/2003, for the renewal of the authorisation of additives for use in animal nutrition.

Keywords: Guidance, renewal, feed additives, characterisation, safety, efficacy

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Introduction

Background and Terms of Reference as provided by the requestor

Regulation (EC) No 1831/2003[1] establishes the rules governing the Community authorisation of additives for use in animal nutrition. Moreover, Regulation (EC) No 429/2008[2] provides detailed rules for the implementation of Regulation (EC) No 1831/2003 as regards the preparation and the presentation of applications as well as the assessment and the authorisation of feed additives.

During the course of the years, the Panel on Additives and Products or Substances used in Animal Feed (FEEDAP Panel) has adopted a series of guidance documents which aim at complementing Regulation (EC) No 429/2008 to help the applicants in the preparation and submission of technical dossiers for the authorisation of additives for use in animal nutrition according to Regulation (EC) No 1831/2003. The FEEDAP Panel has recently updated most of these guidance documents. The most up to date guidance documents cover all aspects from the characterisation of the additives, safety for the target species, consumers and the environment, and the efficacy.

However, the guidance document for the renewal of the authorisations of feed additives (EFSA FEEDAP Panel, 2013) was not included in the last update exercise.

In view of the above, the European Food Safety Authority (EFSA) asks the FEEDAP Panel to revise and update the guidance document for the renewal of the authorisations of feed additives, considering the changes introduced in the other guidance documents, the recent scientific developments and the Panel's experience gained during the last years in the assessment of applications for the renewal of the authorisations. The FEEDAP Panel is also invited to consider initiatives like preparatory info-sessions or public consultations of the draft guidance document. The relevant comments received in either step will have to be considered and addressed in the final version of the guidance document.

Scope of the guidance

This guidance document is part of a series of documents intended to assist the applicant in the preparation and presentation of its application for authorisation of a feed additive, as foreseen in Article 7.6 of Regulation (EC) No 1831/2003. This document does not substitute for the obligation of an applicant to comply with the requirements of Regulation (EC) No 1831/2003 and its implementing rules (Commission Regulation No 429/2008). This document is intended to provide guidance to applicants for the preparation and presentation of an application of the renewal of an authorisation for additives used in animal nutrition. This guidance has four main sections after an introduction. The first one deals with the general principles of the assessment of applications for the renewal of the authorisation of feed additives. Section 2 details the type of information which is required in the different sections of the dossier, while Section 3 provides an overview of common methodologies to fulfil the requirements of Section 2. Finally, Section 4 provides information on the requirements for those applications which include other requests in addition to the renewal.

1. General principles of the assessment of applications for renewal of the authorisation

The main objectives of the renewal of the authorisation of a feed additive are i) the demonstration of compliance of the additive placed in the market with the conditions of the existing authorisation, and ii) the demonstration that in the light of the current knowledge, the additive remains safe under the approved conditions for the target species, the consumers, the users and the environment.

The dossier must enable an assessment to be made of an additive based on the current state of knowledge and permit verification of the compliance of these additives with the fundamental principles for the renewal of the authorisation, which are laid down in Article 14 of Regulation (EC) No 1831/2003.

The information to be submitted and the extent of it will depend on the additive itself and its nature, the category/functional group, the target animals and the conditions of use. The applicant should refer to Regulation (EC) No 429/2008 in order to evaluate which information should be

[1] Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition. OJ L 268, 18.10.2003, p. 29.

[2] 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. OJ L 133, 22.5.2008, p. 1.

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

Reference can be made to published studies to fulfil the requirements listed in the guidance provided that the active substance/agent in literature studies is identical to that under application or, if not, would still allow conclusions on the additive under application to be drawn. In such a case, a justification for read-across should be given.

Studies involving animals should respect the rules on animal welfare laid down by the European Union (EU) legislation, particularly those listed in Directive 63/2010/EU[3]. The use of methods refining or replacing the tests using experimental animals or reducing the number of animals used in these tests shall be encouraged. Such methods must provide the same level of assurance as the methods they aim to replace.

When preparing the application for the renewal of feed additives, the applicant should consider the most up-to-date scientific knowledge (including the most recent assessments of other international scientific bodies), the current scientific/methodological approaches and should follow the most updated guidance documents of EFSA and any other relevant guidance documents. When studies are needed to support the safety or the efficacy of an additive, these should follow the relevant guidance documents of the FEEDAP Panel or other EFSA guidance documents or statements, unless an appropriate justification is provided.

It is recognised that applicants may include in an application for renewal of an authorisation also requests for new uses of the additive (e.g. new target species) as per Article 4 of Regulation (EC) No 1831/2003 and/or modifications of the conditions of authorisation as per Article 13 of that regulation. Although these requests would not be considered strictly as a renewal of an authorisation, they can be addressed in the application for renewal provided that the application to the European Commission reflects the request(s) and the dossier contains all the information necessary for the assessment in line with the requirements detailed in Regulation (EC) No 429/2008 and the applicable guidance documents (see Section 4 of this guidance document).

2. Contents of the technical dossier

Each technical dossier should be stand-alone and contain all the information necessary to allow EFSA to perform an assessment of the application in line with the requirements listed above. The dossier should be structured in accordance with the numbering system proposed in the Regulation (EC) No 429/2008 and comply with the general aspects detailed in Annex II of this Regulation, in particular: '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'. All studies submitted should clearly refer to the same additive (active substance/agent) as the one subject to the application for renewal of the authorisation.

Where the information included in the renewal dossier is substantially the same as that submitted in a previous application already assessed by EFSA, the applicant should clearly indicate (e.g. by using different colours) which parts of the dossier were already submitted, which are updated or modified and which are new.

2.1. Section I – Summary of the dossier

A complete Section I as detailed in Section 10 of Annex 3 of Regulation (EC) No 429/2008 should be submitted. A copy of the original Community authorisation for placing the feed additive on the market, including successive modifications and/or other authorisations of the same additive or the last renewal of authorisation, must be provided. 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 existing authorisation/renewal in terms of identity and safety (and efficacy, when relevant), and a list of all variations (e.g. any changes in the manufacturing process, composition, purity or activity in comparison with the authorised additive) since the original authorisation or the last renewal of the authorisation.

[3] Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes OJ L 276, 20.10.2010, p. 33–79.

2.2. Section II – Identity, characterisation and conditions of use of the additive, methods of analysis

A complete Section II should be provided for each dossier following the provisions of the Guidance on the identity, characterisation and conditions of use of feed additives (EFSA FEEDAP Panel, 2017a) and the Guidance on the characterisation of microorganisms used as feed additives or as production organisms (EFSA FEEDAP Panel, 2018a), if appropriate.

The data provided in this section must allow confirmation of the compliance of the feed additive with the specification detailed in the authorising regulation, including composition, activity, impurities and any other provisions. The applicant is encouraged to apply the most recent and precise analytical methodologies to identify and characterise the additive(s) in accordance with the requirements laid down in Regulation (EC) 429/2008.

The applicant should describe in detail any changes in the manufacturing process, composition, purity (e.g. qualitative and quantitative changes in impurities) or activity in comparison with the authorised additive. The data provided in this section should reflect these changes. As an example, if the modifications made have an impact on the physico-chemical properties of the additive, additional data on the physical properties (e.g. dusting potential, particle size distribution), stability and/or homogeneity should be provided, as appropriate.

If the nature of the changes may have an impact on the safety (e.g. increased bioavailability, higher user exposure) and/or the efficacy of the additive, additional studies may be required to address these aspects.

Recent (not older than one year from the date of submission of the application) analytical data from at least five batches for the composition of the additive and three for the purity should be provided, following the requirements of the guidance documents mentioned above. In case of additives for which there are not enough production batches available during the year previous to the submission of the application, the data should refer to the five (composition)/three (purity) most recent batches.

The applicant should consider the availability of new or up to date analytical methods for the identification and characterisation of the additive, as well as for its purity when providing the information referred above.

For microorganisms used as additives or as production strains, the requirements of the Guidance on the characterisation of microorganisms used as feed additives or as production organisms (EFSA FEEDAP Panel, 2018a) should be followed, in particular for:

- Identification of each microorganism in the light of updated nomenclature,
- antimicrobial resistance/susceptibility,
- antimicrobial production, if not excluded in previous assessments,
- toxigenicity and pathogenicity,
- description of the genetic modification for genetically modified microorganisms,
- absence of viable cells and absence of DNA of the production strain, where relevant, for fermentation products.

For microorganisms qualifying for the qualified presumption of safety (QPS) approach to safety assessment (EFSA, 2007), information should be provided to confirm the compliance with the qualifications listed in the most recent update of the list of QPS-recommended biological agents intentionally added to food or feed as notified to EFSA.[4] If the assessment of the identity and/or qualifications do not confirm the QPS status of the microorganism(s), the applicant should consider the implications for the safety assessment (e.g. need for toxicological studies) and provide data accordingly.

Any new information on incompatibilities or interactions of the additive in premixtures or compound feed with feed materials, carriers, other approved additives or medicinal products since the last assessment should be reported and documented.

The applicant should indicate whether the conditions of use of the additive remain the same as the ones authorised or whether any modifications (e.g. reduction of the minimum concentration in feed, increase of the maximum concentration in feed, change of the withdrawal time) are proposed. In addition, if the applicant proposes new uses of the additive (e.g. new target species), these should be

[4] https://efsa.onlinelibrary.wiley.com/doi/toc/10.1002/(ISSN)1831-4732.QPS

clearly specified. In both cases, the implications for the need of new data/studies to support the safety and/or efficacy of the additive should be considered and addressed in the relevant sections of the dossier, following the provisions of the relevant guidance documents.

With regard to methods of analysis of the active substance (see Section 2.6.1 of Regulation (EC) No 429/2008), if verification studies as specified in this Regulation or the availability of ISO/CEN methods were missing at time of the first application, the applicant should provide that missing information. The same applies for methods of analysis for residues of the additive or of its metabolites in food (see Section 2.6.2 of Regulation (EC) No 429/2008), if applicable.

2.3. Section III – Safety

2.3.1. General requirements

Evidence should be presented that in the light of the current knowledge the additive remains safe under the approved conditions of use for the target species, consumers, users and the environment. An update on the safety covering the period since the original authorisation or the last renewal of the authorisation until 1 year before the date of submission should be presented.

In all the applications for renewal of the authorisation, the following evidence must be provided:

- Results of the post marketing monitoring plan, when such monitoring is included in the authorisation.
- Reports of any adverse effects including incidents/accidents (previously unknown effects, severe effects of any type, increased incidence of known effects) for target animals, consumers, users and the environment. These include any safety related information deriving from any complaint managing system, recalls and other information available in the context of good manufacturing practice and Regulation (EC) No 183/2005[5]. The report(s) on adverse effects should include the nature of the effect(s), number of affected individuals/organisms, outcome, conditions of use, and causality assessment and should consider the use in water for drinking when it is authorised. When an adverse effect is identified, it should be adequately followed up in the relevant section of the dossier (e.g. target species, consumer, user and environment).
- Additional evidence to support the safety of the additive for the target animals, the consumer, the user and the environment should be provided, based on the nature of additive and its use, as described in the following sections.

In order to place all the information above into context, applicants are encouraged to provide quantitative data on the production and on the use of the feed additive per target species/categories and geographical distribution.

2.3.2. Safety for the target species

Evidence should be provided that in the light of the current knowledge the additive remains safe for the target species under the authorised conditions of use.

No additional information to support the safety for the target animals is required for those additives listed in Section 2 of the Guidance on the assessment of the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017b), provided that the qualifications for the exclusion are met.

For those additives authorised for use in feed for all animal species and for which safety was derived from studies in three terrestrial major species, evidence should be provided that the additive is safe for fish (salmonids).

For those additives for which a maximum safe concentration in feed was derived using the results of repeated dose toxicity studies in laboratory animals, the applicant should verify whether new relevant studies are available that would allow identifying a different no observed adverse effect level (NOAEL) or benchmark dose level (BMDL) value than that used to derive such maximum content. In case new toxicity studies are available from which a lower NOAEL/BMDL[6] is identified, a new

[5] Regulation (EC) No 183/2005 of the European Parliament and of the Council of 12 January 2005 laying down requirements for feed hygiene. OJ L 35, 8.2.2005, p. 1.

[6] The updated guidance on the use of the benchmark dose approach in risk assessment (EFSA Scientific Committee, 2017a) should be followed.

calculation of the maximum safe concentration in feed should be done, following the provisions of the guidance on the safety for the target species (EFSA FEEDAP Panel, 2017b).

When modifications in the composition/manufacturing process affect the physico-chemical properties of the additive and may have an effect on the bioavailability of the active substance, implications on the safety for the target species should be addressed following the provisions of the guidance on the safety for the target species (EFSA FEEDAP Panel, 2017b).

When there is knowledge or evidence of adverse effects of the additive in the target species (e.g. reported from the use of the additive (see Section 2.3.1) or from published literature), these should be specifically addressed and the potential implications on the conditions of use of the additive considered.

2.3.3. Safety for the consumer

Evidence should be provided that in the light of the current knowledge the additive remains safe for the consumers under the authorised conditions of use.

No additional information to support the safety for the consumer is required for those additives listed in Section 3.1 of the Guidance on the safety of the consumer (EFSA FEEDAP Panel, 2017c), provided that the qualifications for the exclusion are met.

In all the other cases, the safety update should consider any new data/information available on the absorption, distribution, metabolism and excretion (ADME), deposition and toxicological properties of the additive or its components in the target species or laboratory animals, as well as the exposure of the consumer to residues following the most up-to-date exposure assessment methodology (EFSA FEEDAP Panel, 2017c).

In particular, the aspects detailed in the following sections should be addressed, as appropriate.

2.3.3.1. Residues

Information/data on residues of the additive and or its metabolite(s) in tissues and products of animal origin is required:

a) when the authorising Regulation requires residue monitoring,
b) when there is evidence that the metabolism in the target species may lead to a different set of metabolites/residues compared to that already evaluated,
c) when the modifications in the composition/manufacturing may have an effect on the bioavailability of the active substance,
d) for any additives for which a health-based guidance value (HBGV) is established.

For (b), (c) and (d), the data/information on residues in tissues and products should be provided following the provisions of the Guidance on the safety for the consumer (EFSA FEEDAP Panel, 2017c).

2.3.3.2. Toxicological data/information

Any new information available regarding the toxicological and pharmacological properties of the additive (in laboratory and target animals and in humans) should be provided. When new assessments of the active substance(s)/additive are available from any scientific international bodies (e.g. reassessing HBGV), these should be provided and the implications of the conclusions on the need for any additional studies/data considered.

For those additives for which the original assessment included the evaluation of genotoxicity studies, the compliance of that data set with the requirements of the current guidance (EFSA, 2011; EFSA FEEDAP Panel, 2017c) should be confirmed. In particular, the following aspects should be carefully considered in line with the opinion of the Scientific Committee on the 'Clarification of some aspects related to genotoxicity assessment' (EFSA Scientific Committee, 2017b), namely:

- The unscheduled DNA synthesis (UDS) assay is currently considered of low sensitivity, if compared with other *in vivo* experimental approaches that have been validated in the last few years. For this reason, when existing data are re-evaluated, only positive results are considered adequate to assess genotoxic potential, while in case of negative outcome the reliability and significance of the study should be carefully evaluated in a weight of evidence approach, before deciding whether more sensitive tests such as transgenic rodent somatic and germ cell gene mutation assay or *in vivo* comet assay would be needed to complete the assessment. The UDS test is no longer recommended as an *in vivo* follow-up to positive results in *in vitro* gene mutation tests.

– In case of negative results in an *in vivo* genotoxicity test, evidence of target tissue exposure is necessary (for details see EFSA Scientific Committee, 2017b).

If the set of genotoxicity studies submitted in the original dossier would not rule out the genotoxic potential of the substance/additive, additional testing following the most recent guidance would be necessary.

Special attention should be given on the assessment of the genotoxicity of chemical mixtures, considering the Statement of the EFSA Scientific Committee on genotoxicity assessment of chemical mixtures (EFSA Scientific Committee, 2019), in particular:

- The first step must be to characterise the mixture as fully as possible.
- For fully defined mixtures, the EFSA Scientific Committee recommends applying a component-based approach, i.e. assessing all components individually using all available information including read across and (quantitative) structure–activity relationship (QSAR) considerations about their genotoxic potential.
- For mixtures containing a substantial fraction of substances that have not been chemically identified, the EFSA Scientific Committee recommends that first the chemically defined substances should be assessed individually for their potential genotoxicity (see above) and then, if these prove negative, the genotoxic potential of the unidentified fraction should be evaluated to complete the assessment of the mixture. Experimental testing of the unidentified fraction or, if it is not feasible, testing of the whole mixture should be undertaken.

It needs to be considered whether the assessment of all the new evidence on the toxicological profile of the additive/active substance from the above would allow to set a health-based guidance value or would lead to the modification of an existing one.

2.3.3.3. Exposure

For all the additives for which a HBGV is already established, consumer exposure, following the provisions of the Guidance on consumer safety (EFSA FEEDAP Panel, 2017c), should be assessed. This exposure assessment should be based on the most recent residue data available, as appropriate (see Section 2.3.3.1).

In addition, any data on residues in food of animal origin deriving from uses of the active substance other than as a feed additive (e.g. medicinal products) should be considered in the exposure assessment.

Any new information on the exposure of the consumer to residues of the additive or its metabolites via sources other than food of animal origin should be provided.

2.3.4. Safety for the user

Evidence should be provided that, in the light of the current knowledge, the additive remains safe for the user under the authorised conditions of use. Special consideration should be given to:

– Experience in the manufacturing plant may be used to provide 'real-life' evidence of effects of the additive to people directly exposed to the additive. To this end, applicants should include in the dossier records on the adverse effects on the workers of the manufacturing plant and any other information on adverse effects to persons exposed to the additive that may be identified and made available to the applicant via the complaint management system.
– The available information for the additive or its components (if a mixture) or main impurities evaluated for the classification and labelling purposes according to Regulation (EC) No 1272/2008 (CLP), including, when available, the outcome of the assessment under Regulation (EC) 1907/2006 (REACH) or other regulations.

When the data set submitted for the original assessment leading to the authorisation of the additive contained a complete assessment of the safety for the user, the application for renewal may be limited to the new evidence available since the last authorisation/renewal.

When the original data set was not complete and did not allow the Panel to perform a complete assessment of the safety of the additive for the user, the application for renewal should address the data gaps in the former submission, in line with the requirements of the Guidance on the safety for the user (EFSA FEEDAP Panel, 2012).

For additives for which a change in the manufacturing process/composition leads to a change in the physical properties of the additive, additional studies may be needed. The need for and type of studies

will depend on the changes in exposure (i.e. route and/or extent) and/or potential new hazards introduced.

2.3.5. Safety for the environment

Evidence should be provided that, in the light of the current knowledge, the additive remains safe for the environment under the authorised conditions of use.

No additional information on the safety for the environment in the framework of the renewal of authorisation is needed for the following additives, provided that the qualifications for the exclusion are met:

- Additives intended to be used in feed for non-food-producing animals only,
- Natural substances already present in feedingstuffs or that would not increase their concentration in the environment,
- Additives extensively metabolised in the animal or rapidly degraded in nature,
- Additives consisting of microorganisms that qualify for the QPS approach to safety assessment,
- Additives consisting of microorganisms naturally present in soil, plants or gastrointestinal tract of the animals.

For those additives not exempted above, applicants should refer to the Guidance on the assessment of the safety of feed additives for the environment (EFSA FEEDAP Panel, 2019) to assess whether the additive remains safe under the current requirements and to assess whether new data/ information would be required.

2.4. Section IV – Efficacy

Efficacy studies are not required for the renewal of the authorisation of feed additives except:

- In the case of coccidiostats and histomonostats, new studies are required to obtain a contemporary confirmation of efficacy. Evidence of the maintained susceptibility of recent (not older than 3 months at the time of study start) strains of *Eimeria* spp. and *Histomonas meleagridis* to the coccidiostat and histomonostat, respectively, should be provided in the form of sensitivity studies (with at least three sources (origins, farms) of *Eimeria/Histomonas* strains (mixed infection)). These studies should have been completed within the last 2 years before the submission of the application and should follow the requirements of the Guidance on the assessment of the efficacy of feed additives (EFSA FEEDAP Panel, 2018b).
- When the applicant proposes amending or supplementing the conditions of the original authorisation which may have an impact on the efficacy of the additive (e.g. a reduction of the minimum recommended dose), additional efficacy studies may be required. In that case, the requirements of the Guidance on the assessment of the efficacy of feed additives (EFSA FEEDAP Panel, 2018b) should be followed.

2.5. Post-market monitoring

When a post-market monitoring plan was undertaken as a result of the original authorisation or the last renewal of authorisation, the results of this plan should be reported under Section III.

If the applicant includes a proposal for amending or supplementing the conditions of the original authorisation regarding the conditions concerning future monitoring, this should be clearly described.

3. Means to provide evidence of safety (and efficacy, when relevant)

Applicants should assess which is the best means to provide evidence of the safety (and when relevant, efficacy) of the additive subject to the application for renewal of the authorisation, as required in the previous sections. The following sections detail common approaches that can be used to retrieve the information in addition to the mandatory requirements listed in Section 2.3.1. However, applicants may choose to submit other types of information/evidence provided that they fully address the requirements above and are properly justified.

3.1. Extensive literature searches

An extensive literature search (ELS) may provide information on the safety of the feed additive under the authorised conditions of use. The analysis of the data must establish that the active substance(s)/agent(s) in literature studies is (are) identical to that under application or, if not, would still allow conclusions on the additive under application to be made[7]; for additives produced by fermentation, it should include the production strain(s). For additives consisting of a mixture, the extensive literature search should cover all the components of the mixture (individually and the complete mixture).

The ELS should cover at least the period since the last assessment until not more than 1 year before the date of submission of the application for renewal. ELS should be methodical, transparent and reproducible. The review question should be clearly stated and the corresponding key elements defined. The whole process should be properly documented and reported (Glanville et al., 2014).

Applicants should follow the recommendations of the Technical manual for performing electronic literature searches in food and feed safety (Glanville et al., 2014) when performing the searches.

Relevant information sources should be searched in a structured manner. The applicant should make reasonable efforts to locate all sources of relevant information and provide reasons for the selection of such sources. At least two bibliographic databases (including at least agricultural/ aquacultural and medical/veterinary databases) which record documents such as journals, reports, conference proceedings and books should be searched. In addition, the search should consider sources other than bibliographic databases, such as reference lists of full-text journal articles (e.g. reviews), websites of conferences or organisations.

Special attention should be paid to the search terms and search strategy used to ensure the sensitivity of the search. Search strings should be broad enough to yield studies on the relevant end-points with regard to the safety for the target animals, consumers, users and environment detailed in the relevant guidance documents, and should include any specific known (adverse) effects (e.g. genotoxicity, endocrine effects) of the additive.

To design a sensitive search strategy, searchers should employ a combination of indexing terms (controlled vocabulary) when available (selected from the indexing language or thesaurus) and a wide range of free-text terms (or natural vocabulary). When choosing free-text terms to use in a search strategy the reviewer should consider as many synonyms and related terms as possible. It is important to consider differences in spelling and terminology, use of abbreviations, identification numbers (e.g. CAS number, FLAVIS), use of the generic and brand names of the additive. Appropriate Boolean operators, truncation, wildcards or proximity operators should be used.

The search methodology should be documented and reported in detail to ensure transparency and enable the evaluation and replication of the search:

For database searches:

- the name of the database and the service provider used;
- the date of the search and the date range searched;
- any limits placed on the search such as language or publication status;
- the full search strategy (all terms and set combinations) and the number of records retrieved.

For sources other than bibliographic databases:

1) Websites and journal table of contents
   - the name of the resource (i.e. website name, the journal name in case of searching in specific tables of contents);
   - the URL (uniform resource locator, the internet address);
   - the date on which the search was conducted and the date range of the search, or the dates, volumes and issues in the case of table of contents;
   - the method of searching, e.g. browsing, using the search engine or scanning tables;
   - any limits applied to the search (e.g. publication types);
   - the search terms used and the number of relevant summary records or full-text documents retrieved.

[7] The literature search could also be used to provide justifications for the read-across.

2) References lists
   - the bibliographic details of the documents whose reference lists were scanned;
   - the number of relevant bibliographic references retrieved.

Once the search is completed and duplicate publications have been removed, the retrieved publications should be assessed for their relevance by at least two reviewers in parallel. Relevance reflects the extent to which the study is appropriate to assess the safety (and when relevant, efficacy) of the additive subject to the application. The selection process will assess the studies against inclusion/exclusion criteria clearly defined *a priori*.

The following information concerning the selection of publications should be clearly reported:

- Exclusion and inclusion criteria applied to the papers retrieved,
- Expertise and number of the reviewers involved in the selection process,
- Description of stages of the selection process (e.g. stepwise approach with a first stage assessing title and abstract and a second assessment based on the full text),
- Final number of papers reviewed and excluded papers on each stage of the selection process, if applicable, with reasons for exclusion. The applicant is encouraged to describe the flow of information through the different phases of the process using the relevant parts of the PRISMA flow diagram,[8]
- A list of the bibliographic references for all relevant publications selected,
- A list of the bibliographic references for the unobtainable publications (if any), with explanation why could not be obtained.

Applicants should provide a summary table of the outcome of the selection process where the relevant studies are described. The summary table should include, as a minimum, information on the test item (and relation with the product under assessment), concentration/doses, animal species (as appropriate), duration, end-points assessed and summary of the effects observed.

In addition, the applicant should provide a critical assessment, by means of a summary text, of the evidence collected and explain how it supports the conclusions reached.

The list of relevant references included should be provided in 'RIS'[9] or an equivalent format compatible with EndNote. Copies of all relevant published scientific data should be provided as mentioned in Section 2 'Contents of the technical dossier'. The applicant must ensure that terms and conditions asserted by any copyright holder of publications or information submitted to EFSA are fully satisfied. The applicant should consult with copyright licensing authorities (i.e. at national level) for guidance on purchasing copyright licenses to reproduce any publications provided to EFSA. The applicant remains solely responsible and liable for obtaining all necessary authorisations and rights to use, reproduce and share the publications provided to EFSA.

3.2. New studies

The applicant may choose to submit new experimental studies to provide evidence on any aspects of the safety of the additive and, if relevant, of its efficacy. Such studies should be performed and reported according to the relevant guidance documents in force at the time of the submission of the application.

For studies for the safety for the target species, these should be completed within the 3 years before the submission of the application and should reflect the current EU farming/production conditions.

4. Other requests linked to the application for the renewal of the authorisation

It is recognised that an application for the renewal of an existing authorisation can be used to propose modifications to the existing authorisation (modification of the conditions of use, as per Article 13 of Regulation (EC) No 1831/2003) or the request for the authorisation for new uses of the feed additive (e.g. new target species, as per Article 4 of Regulation (EC) No 1831/2003). When the application for renewal contains requests for the modification of the conditions of the authorisation or

[8] http://www.prisma-statement.org/PRISMAStatement/FlowDiagram.aspx

[9] RIS is a standardised tag format that enables the exchange of bibliographic information. It is supported by a number of reference manager software.

new uses of the feed additive, all the aspects related to characterisation of the additive and its conditions of use, safety and efficacy, where relevant, linked to such modifications/new uses should be addressed following the relevant guidance documents applicable at the time of the submission of the application.

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Abbreviations

ADME	absorption, distribution, metabolism and excretion
BMDL	benchmark dose level
CAS	chemical abstracts service
CEN	European Committee for Standardization
CLP	classification, labelling and packaging regulation
ELS	extensive literature search
FLAVIS	The EU Flavour Information System
HBGV	health-based guidance value
ISO	International Organization for Standardization
NOAEL	no observed adverse effect level
QPS	qualified presumption of safety
QSAR	(quantitative) structure-activity relationship
REACH	registration, evaluation, authorisation and restriction of chemicals
UDS	unscheduled DNA synthesis
URL	uniform resource locator