STATEMENT

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Analysis of the need for an update of the guidance documents

EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP)

Abstract

The EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP Panel) adopted a series of guidance documents which complement the Regulations governing the authorisation of feed additives. These are intended to help applicants in their preparation of technical dossiers. Although most guidance documents prepared by the Panel have been updated at some point, experience has shown that some elements are in need of technical update. Consequently, the EFSA has asked the FEEDAP Panel to identify from the current guidance documents those that need to be updated. The FEEDAP Panel addressed this by considering the experience gained since the last major revision of the individual guidance documents. Each of the Standing Working Groups of the FEEDAP Panel were asked to identify issues which have arisen during additive assessments and which suggested the need for elements of the guidance to be reconsidered. In addition, consideration was given to the relevant overarching guidance documents produced by the EFSA Scientific Committee and to developments in assessment tools provided by EFSA and other international organisations. The analysis of the information collected indicated a number of broad areas in the existing guidance which need possible revision. In particular, since the existing guidance on environmental risk assessment is no longer aligned to other EFSA outputs, the Panel proposes that revision of this guidance should be given the highest priority. The Panel then proposes the revision of the three guidance documents concerned with safety (target animals, consumer and user) followed by the guidance on efficacy. In parallel, the data necessary to establish the characterisation of the additive should be reviewed and modified as necessary. The FEEDAP Panel considers it fundamental to involve industry, consumer associations and experts from Member States risk assessment bodies in the early stages of the guidance revision.

Keywords: guidance revision, safety, efficacy, feed additives

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1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

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

The Panel on Additives and Products or Substances used in Animal Feed (FEEDAP Panel) has adopted a series of guidance documents which complement 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.

Most guidance documents prepared by the Panel have been updated at some point after their first adoption, sometimes extensively and sometimes simply introducing revisions made necessary by changes to the implementing rules. Others have never been reviewed or updated. Table 1 lists the most recent version of the guidance documents adopted by the FEEDAP Panel.

Table 1: List of the most up-to-date guidance documents adopted and used by the FEEDAP Panel

Guidance	Date of publication
Update of the Guidance for the preparation of dossiers by categories of feed additives – Technological additives (EFSA-Q-2010-00902 & EFSA-Q-2010-00017)	18/1/2012
Update of the Guidance for the preparation of dossiers by categories of feed additives – Sensory additives (EFSA-Q-2010-01157)	18/1/2012
Update of the Guidance for the preparation of dossiers by categories of feed additives – Nutritional additives (EFSA-Q-2010-01158)	18/1/2012
Update of the Guidance for the preparation of dossiers by categories of feed additives – Zootechnical additives (EFSA-Q-2010-01159)	18/1/2012
Update of the Guidance for the preparation of dossiers by categories of feed additives – Coccidiostats and Histomonostats (EFSA-Q-2010-01160)	24/5/2011
Update of the Technical guidance on tolerance and efficacy studies in target animals (EFSA-Q-2010-01163)	23/5/2011
Technical guidance: Microbial Studies (EFSA-Q-2008-461)	21/10/2008
Update of the Technical guidance on consumer safety (EFSA-Q-2010-01161)	18/1/2012
Update of the Technical guidance on user safety (EFSA-Q-2010-01162)	18/1/2012
Technical guidance: Environmental risk assessment (EFSA-Q-2008-408)	29/10/2008
Guidance for the re-evaluation of certain additives already authorised under Directive 70/524/EEC (EFSA-Q-2008-410)	23/9/2008
Technical guidance: Extrapolation of data from major species to minor species (EFSA-Q-2008-409)	23/9/2008
Update of the Technical guidance: Additives already authorised for use in food (EFSA-Q-2011-01095)	18/1/2012
Guidance on the compatibility of zootechnical microbial additives with other additives showing antimicrobial activity (EFSA-Q-2007-174)	12/3/2008
Guidance on the assessment of bacterial susceptibility to antibiotics of human and veterinary importance (EFSA-Q-2011-01108)	4/6/2012
Technical Guidance document for the assessment of additives intended to be used in pets and other non food-producing animals (EFSA-Q-2010-01226)	10/2/2011
Update of Guidance on the assessment of the toxigenic potential of *Bacillus* species used in animal nutrition (EFSA-Q-2013-00303)	5/5/2014
Guidance document for the renewal of the authorisation of feed additives (EFSA-Q-2012-00962)	22/10/2013
Guidance on the safety assessment of *Enterococcus faecium* in animal nutrition (EFSA-Q-2011-01173)	23/5/2012
Guidance for the assessment of biomasses for use in animal nutrition (EFSA-Q-2010-00939)[(a)]	25/3/2011

(a): The guidance for the assessment of biomasses for use in animal nutrition is not linked to the assessment of feed additives but shares many commonalities, and therefore, changes in the other guidance documents may have an impact on this guidance.

The European Food Safety Authority (EFSA) asks its FEEDAP Panel to:

1) identify from the current guidance documents listed above, those that need to be updated, taking into consideration the most recent scientific developments and the experience gained in the assessment of feed additives;
2) update the guidance documents in need of revision accordingly; this activity can be conducted in different rounds of activities on the basis of the priorities identified and on the feasibility of the revision according the resources available;
3) taking into account the sensitivity and the relevance of some of the guidance documents under revision and the entity of the revision itself (e.g. substantial or not), consider initiatives like preparatory info-sessions or public consultations of the draft guidance documents. The relevant comments received in either step will have to be considered and addressed if appropriate in the final version of the guidance documents.

The present output addresses only the first of the three terms of reference. The second and third terms of reference will be addressed when the relevant guidance documents, as identified in this output, will be updated.

2. Methodology

The FEEDAP Panel addressed the first term of reference by considering the experience gained from the high number of applications which have been assessed since the last major revision of the individual guidance documents. To this end, each of the Standing Working Groups of the FEEDAP Panel were asked to identify issues which have arisen during these assessments and which suggested the need for elements of the guidance provided to applicants to be reconsidered.

In addition, the Panel is aware of the overarching guidance documents developed by EFSA Scientific Committee and of the developments in assessment tools from EFSA (e.g. comprehensive food consumption database, statistical reporting) and from other organisations (e.g. EMA, ECHA, WHO/FAO, OECD), which will have to be considered in the update of the guidance documents.

The views of third parties (European Commission, industry) expressed, for example, in the course of face to face meetings, teleconferences, responses to FEEDAP opinions and other correspondence were also considered when assessing the need to modify existing guidance documents.

3. Assessment of the need to update

The analysis of the information collected by the methods described above indicated several broad or fundamental elements in the guidance provided to applicants which need reconsideration and possible revision. The main issues identified are listed below following the structure of Annex II of Regulation (EC) No 429/2008.

Identity, characterisation and conditions of use of the additive

There is a need for a clear definition/characterisation of what constitutes an active substance and the relationship between active substances/agents and blended formulations (additives, premixtures, preparations).

There is a need for clarification of the data needed to adequately describe the composition of additives from some categories or functional groups of additives (e.g. data on X-ray diffraction for clays, Fourier transformed infrared spectroscopy (FTIR) for chelates).

Consideration should be given to the impact of new methodologies in manufacturing and processing (e.g. nanomaterials, ultrafiltration) when determining the data needs for safety assessment.

The hazard analysis and critical control points (HACCP) plan and evidence of external auditing should be included as part of the description of the manufacturing process.

The relevance of some data requirements for additives not linked to a holder of authorisation should be considered. In particular, the value of collecting data on purity/impurities (unless included if as part of specifications) and on particle size and dusting potential is open to question in the absence of a specific formulation.

Safety

There is the need to ensure consistency of the approach for the assessment of fermentation products occurring in different categories of additives (e.g. GMM vs non-GMM, (need for)

assessment of antimicrobial resistance and presence of DNA from the production strain, endotoxin production for Gram-negative bacteria, production of secondary metabolites, purity relative to inclusion rate).

Given the continuing development of resistance among clinical strains of bacteria to antibiotics and the changing effectiveness of antibiotics, there is a possible need to revisit the battery of antibiotics tested and the list of microbial species for which cut off values are proposed.

The safety assessment of botanicals should be revised based on the experience gained directly with preparations containing botanicals and from the assessment of individual compounds found in botanical extracts.

Safety for the target species

The statistical analysis of the data of tolerance studies used to assess target animal safety is presently based on the absence of differences which does not indicate the equivalence of the effects. Therefore, the statistical evaluation of tolerance studies should be based on an assessment of equivalence.

The experimental design of safety studies for target species should consider the potential for a reduction in the number of animals/animal studies (e.g. by the application of the benchmark approach, selection of more relevant endpoints, combination of different studies, simultaneous testing of multiple substances).

A derivation of target animal safety from data obtained from studies with laboratory animals is established in the guidance for sensory additives and the guidance for additives already authorised in food. To reduce experiments with animals, this principle could be applied to other types of additives. If so, consideration should be given to the relevance of toxicological data/end points obtained from such studies.

There is a need to review the default values of body weight and feed intake for the target species to more closely align with current European production practices and progress in breeding. This should include a review of the categories of target animals needed to establish safety and efficacy taking into consideration the intended purpose of the additive. The minimum duration of studies should be modified accordingly.

The appropriateness of using a comparison of human exposure and animal exposure in the assessment of safety for target species given additives already authorised in food should be reconsidered.

Safety for the consumer

There is a need for a reconsideration of the relevance of toxicological studies for fermentation products considering the nature and history of the production strain and the production process.

The food consumption model used to assess the contribution of residues from animal products to consumer exposure should recognise the most recent pan-European data from the EFSA comprehensive European food consumption database, and consider the possibility of including data for specific countries and population groups.

Safety for the user

For additives not linked to a holder of authorisation, it should be considered whether the assessment of user safety could be restricted to systemic effects, which are linked to the active substance/agent, and not to specific aspects linked to formulations which are not subject of the authorisation.

The approach to user safety taken by ECHA for individual compounds and that applied to holder specific additives should be harmonised whenever possible.

Safety for the environment

The guidance on environmental risk assessment should be completely revised in order to take account of new developments in methodology and the extensive documentation produced by the EFSA Scientific Committee and other bodies (e.g. EMA, OECD).

Efficacy

Consideration should be given to the inclusion of specific endpoints needed for the experimental demonstration of efficacy for all categories/functional groups, including those newly introduced.

For coccidiostats, there is a need to review the number and type of trials necessary to support efficacy.

General aspects

A detailed description of use and reporting appropriate statistical methods (e.g. for target animal safety, toxicology, residue determination at certain withdrawal points, dose titration in efficacy studies) should be given. The value of meta-analysis for the assessment of efficacy should be reconsidered. In addition, the FEEDAP guidance documents should be aligned with the EFSA guidance on statistical reporting.[1]

There is a need to incorporate the potential to use newly validated and internationally recognised methods (e.g. OECD technical guidelines for user safety, comet assay, QSAR toolbox for prediction of genotoxicity) into the appropriate guidance documents.

The issues listed above imply the need for a substantial revision of the following guidance documents:

- Guidances for the preparation of dossiers by categories of feed additives: Technological additives, Sensory additives, Nutritional additives, Zootechnical additives and Coccidiostats and Histomonostats.
- Technical guidance on tolerance and efficacy studies in target animals, microbial studies, consumer safety, user safety, environmental risk assessment.
- Technical guidance on extrapolation of data from major species to minor species, additives already authorised for use in food, on the assessment of bacterial susceptibility to antibiotics of human and veterinary importance and the assessment of additives intended to be used in pets and other non food-producing animals.

The Guidance document for the renewal of the authorisation of feed additives and that for the assessment of biomasses for use in animal nutrition also may require updating in the light of changes introduced elsewhere.

In addition to the general points considered above, other more minor aspects were identified which would require additional consideration in the update of specific guidance documents. The update of all of the guidance documents will recognise the availability and application of new methodologies and improvements in conducting and reporting of studies.

The guidance for re-evaluation does not need to be revised/updated as all relevant applications have been submitted. The Panel does not see the need for the time being to update the guidance documents on the assessment of the safety of *Bacillus* spp. and *Enterococcus* spp., as these documents were adopted/updated recently and, to the knowledge of the Panel, there is no new information that would justify their revision. Similarly, the Panel does not see the need to update the guidance on compatibility of zootechnical additives with substances showing antimicrobial properties.

Depending on the outcome of the revision of the guidance documents, there may be a need to change the overall structure of the guidance provided. For example, it may be advantageous to separate the existing guidance on tolerance and efficacy and to have a specific guidance for the characterisation of the additives.

4. Priority

As the existing guidance on the environmental risk assessment has been found to be in need of technical update, the Panel proposes that the revision of this guidance should be given the highest priority and a specific working group should be established for this purpose.

The Panel would then give priority to the remaining three guidance documents concerned with safety for target animals, the consumer and the user followed by the guidance on efficacy. In parallel, the data necessary to establish the characterisation of the additive should be reviewed and modified as necessary. Such modifications could be inserted in the appropriate section of the guidance for each category of additive or may lead to the creation of a separate guidance. These elements of the work will be made by the existing working group on guidance update, augmented as necessary by specific expertise.

At this stage, it may be possible to determine whether all of the existing guidance documents need to be maintained or whether the number of guidance documents could be reduced by, for example, omitting the guidance documents for the additive categories.

[1] European Food Safety Authority, 2014. Guidance on Statistical Reporting. EFSA Journal 2014;12(12):3908, 18 pp. doi:10.2903/j.efsa.2014.3908

The remainder of the guidance documents would be updated subsequently either by the existing working group or by specific ad hoc working group(s) as appropriate.

5. The way forward

The FEEDAP Panel considers it fundamental to involve industry and consumer associations and experts from Member States risk assessment bodies in the early stages of the guidance revision. The FEEDAP Panel will share this document with relevant stakeholders in advance of an info session to be held in July 2016. Stakeholders will have the opportunity either to submit written comments in advance of the info session or to discuss it during the meeting itself. The feedback received will be considered for integration into the revision of the guidance documents.

Ultimately, it is intended that public consultations will be held for those guidance documents which are central to the assessment of all categories of additives and for which substantial revisions have been made.

Abbreviations

ECHA	European Chemicals Agency
EMA	European Medicines Agency
FAO	Food and Agriculture Organization
FEEDAP Panel	EFSA Panel on Additives and Products or Substances used in Animal Feed
GMM	genetically modified microorganisms
HACCP	hazard analysis and critical control points
OECD	Organisation for Economic Co-operation and Development
QSAR	quantitative structure–activity relationship models
WHO	World Health Organization