Proposed Changes to EU Regulations on Feed Additives

Author
***Tamsin Dawson**, Project Associate - Regulatory Affairs, Triveritas Ltd.*

Keywords/Abbreviation List
Feed additives; European Union; Regulations; Guidelines; Quality; Safety (Tolerance); Efficacy; European Food Safety Authority; FEEDAP Panel; Stakeholders.

Abstract
The establishment of a regulatory framework for the assessment and authorisation of feed additives placed on the market in the EU for animal use began in the early 1970's. This legislative framework is entirely independent of the regulations governing veterinary medicinal products. Feed additives for animal use are legislated under one core regulation in the EU and a handful of supporting regulations. Guidance documents, produced by the European Food Safety Authority (EFSA), are available to assist the applicant in fulfilling the requirements laid down in the regulations. However, as heard at an EFSA Meeting with Stakeholders on Feed Additive Applications (July 2016, Brussels), experience gained in assessing applications has highlighted that these documents can be ambiguous, and in places data requirements can be inappropriate for certain categories of feed additives. Scientific progress in the field of feed additives has therefore prompted a revision of one of the regulations, and all the guidance documents, to reduce ambiguity and define better endpoints for data collection.

Introduction

Feed additives for use in animal feed are substances, micro-organisms or preparations, other than feed material and premixtures, which are intentionally added to feed or water in order to favourably affect the characteristics of the feed, animal performance or animal products. Five main categories of feed additives are recognised under current EU law, as outlined in Table 1.

The regulatory framework for feed additives is entirely independent of the regulations governing veterinary medicinal products. In the EU, additives for use in animal feed are legislated under two main regulations:

- Regulation (EC) No 1831/2003[1] of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition.
- Commission Regulation (EC) No 429/2008[2] of 25 April 2008 on detailed rules for the implementation of Regulation (EC) No 1831/2003[1] 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.
- [Three further regulations are relevant under the regulatory framework, covering reference laboratories, reference samples, and the placing on the market of feed.]

Regulation 1831/2003[1] outlines the rules for authorising the placing on the market and use of feed additives with the aim of protecting human health, animal health and welfare, users, consumers and the environment. Requirements for labelling and packaging of feed additives and premixtures are outlined, as well as an overview of the authorisation procedure and timelines.

In support of the first mentioned regulation, Regulation 429/2008[2] outlines the general and specific requirements to be satisfied in the application "dossier". Similar to the format of an EU dossier for veterinary medicinal products, a feed additive technical dossier is split into four "sections" that cover 1) Summary of the Dossier (information on the applicant and scope of the product); 2) Qualitative and Quantitative Composition (including manufacturing process and quality control processes); 3) Safety of the feed additive; 4) Efficacy of the feed additive.

Table 1: Categories of Feed Additives.

Category	Definition	Examples
Technological	Any substance added to feed for a technological purpose.	Preservatives, antioxidants, stabilisers, acidity regulators.
Sensory	Any substance, the addition of which to feed improves or changes the organoleptic properties of the feed, or the visual characteristics of the food derived from animals.	Colourings and flavourings.
Nutritional	Any substance, the addition of which to feed satisfies the nutritional needs of the animal.	Vitamins, trace elements, amino acids.
Zootechnical	Any additive used to affect favourably the performance of animals in good health or used to affect favourably the environment.	Digestibility enhancers, gut flora stabilisers.
Coccidiostats and Histomonostats	A substance intended to kill or inhibit protozoa.	Ionophores

The scientific assessment of feed additive applications is the responsibility of the European Food Safety Agency (EFSA) and more specifically the FEEDAP Panel. Successful applications are published in the Commission's European Union Register of Feed Additives. The FEEDAP Panel have produced up to 20 guidance documents to aid the applicant in fulfilling the requirements laid out in the regulations. Unlike veterinary medicinal product development and registration procedures, no scientific advice or pre-submission meetings are currently offered by EFSA, therefore the applicant is reliant on the guidance provided in FEEDAP guideline documents. Some of these guidance documents however were written before an actual dossier or re-evaluation dossier was reviewed by the panel (particularly for technological and sensory additives), and therefore certain conditions are considered to be ambiguous or inappropriate.

Proposed changes to both Regulation no. 429/2008[2] and the FEEDAP guidance documents were outlined at an EFSA meeting with Stakeholders on Feed Additive Applications (held on the 14th and 15th July 2016 in Brussels), which promises more specific direction when developing and registering feed additives in the EU

Proposals on the amendment of Regulation (EC) No. 429/2008

In September 2015, the EU Commission provided an initial draft to amend Regulation (EC) 429/2008[2] as regards 'the preparation and the presentation of applications and the assessment and the authorisation of feed additives'[3]. Updates were to consider a more harmonised approach to data protection/confidentiality during and post the procedure e.g. provision of supplementary information following an inconclusive EFSA opinion. Stakeholders voiced at the meeting that applicants are essentially producing data for the competition (non-holder specific registrations), therefore improved data protection in the regulation update is fundamental. Alignment of terminologies with EFSA risk assessments (amongst other Annex changes) was also the essence of the change.

Dr Marta Ponghellini, of the Animal Nutrition Unit at the European Commission (EC), presented a session at the EFSA meeting on the feedback and views of the EC on the regulation proposals. Dr Ponghellini started by saying that amendments to regulation 429/2008[2] are a joint effort between the EC, EFSA, the 28 EU member states, EU Reference Laboratory for Feed Additives (EURL-FA), and consultation with stakeholders. The proposals are essentially making changes to every Annex of the regulation, including:

- **Annex I** - review of the application form to simplify and reduce repetition. The provision of an entirely new annex (termed "monograph") may be implemented to provide an overview of the additive including; identity, function, specifications of the active substance, physico-chemical properties of the additive, MRLs, other characteristics suitable for identification of the additive, and conditions of use. This overview is not dissimilar to that required in the application form for a veterinary medicinal product submission in the EU.
- **Annex II** - technical dossier covering quality, safety and efficacy. Amendments intend to be updated in line with related EFSA guidance.
    - *Quality* - identity of the additive will consider, amongst many changes, more specific direction for analytical methods; a new nanoparticle section; and stability criteria.
    - *Safety* - recommendations for amendment include demonstration of safety by identification or the most sensitive species; criteria for extrapolating data between different species e.g. cattle to sheep, and between categories of species e.g. dairy to beef; tolerance tests for some species (considering animal welfare issues); and changes to the user safety risk assessment.
    - *Efficacy* - similar to safety proposals, amendments may include extrapolation of data between species and categories of species; requirements for demonstration of efficacy in liquid feed and in water; criteria for efficacy tests to be better defined; and criteria/new rules for new functional groups to be developed.
- **Annex III** - specific requirements to be satisfied in the dossier with respect to certain categories of additives. Revisions to this section may include new functional groups; revision of silage additives (alignment to other technological additives); development of general criteria for the efficacy studies (more transparency and predictability); and a new approach for innovative additives. Specific sections to this Annex are intended to be revised to improve criteria for non-holder specific authorisations; better definition of the part of the dossier considered essential for the renewal procedure; and revision of the re-evaluation procedure.
- **Annex IV** - this annex covers categories and definitions of target animals and indication of the minimum duration of efficacy studies. The revision of this Annex aims to improve the definition of some species/categories, including minor species, pets and non-food producing animals; revise the present species for zootechnical parameters and physiological parameters; and redefine the categories in general.

A draft legislative proposal for first discussion by the EC Standing Committee was estimated for September 2016, following which consultation with stakeholders would take place. However during the meeting of the Animal Nutrition & Veterinary Medicines (ANVM) Section of the Standing Committee on Plants, Animals, Food and Feed (SCoPAFF) held on 12th to 13th September 2016, it was declared that limited time was available to discuss this aspect. There has been no further news on this at the time of this article going to print. Finalisation of the amended Regulation is anticipated within the next 4 years.

FEEDAP guidance documents

Professor Andrew Chesson of the FEEDAP panel presented a session at the EFSA/Stakeholder meeting on the revision of the guidance documents.

The FEEDAP panel has produced 19 guidelines to date to assist applicants in addressing the data requirements to build an application dossier in line with Regulation 1831/2003[1] and 429/2008[2]. The latest updates to these guidance documents were adopted in 2011. A further guideline is currently in preparation that considers Genetically Modified Microorganisms (GMM).

With the admission that current guidelines need to be updated due to scientific progress in the field and experience gained from assessing 'real' dossiers, two further principle elements were found to drive a need to revise many of the existing documents. The novelty in additive design has introduced products with properties not considered when developing the present guidelines. In addition, the introduction of new or modified assessment techniques from within EFSA or from other recognised bodies (e.g. The Organization for Economic Cooperation and Development (OECD), European Chemicals Agency (ECHA) and European Medicines Agency (EMA)) has prompted a need to modify these documents.

The current guidelines are structured in a way that presents 5 "vertical" guidelines on each feed additive category (outlined in Table 1 above), and 14 "horizontal" guidelines written on aspects for each category e.g. guidance on: tolerance and efficacy studies in target animals; microbial studies; consumer safety; user safety; environmental risk assessment; extrapolation to minor species etc. Alternative organisation styles of guideline framework were proposed. However, industry feedback during the meeting was to remain with the current presentation style for the pending updates.

Guidance documents are to be revised in the following order of priority (work has already started on the Environmental Risk Assessment guidance):

1. **Environmental Risk Assessment (ERA)**
   The current ERA version is considered to not be consistent with approaches within EFSA & other bodies assessing the environmental impact of chemicals under frameworks such as: Registration, Evaluation, Authorisation & restriction of Chemicals (REACH), Plant Protection Products (PPP), Biocides, and Veterinary Medicinal Products. Phase I of the risk assessment should also be revised so that the decision tree distinguishes between high-risk (e.g. coccidiostats, heavy

metals) and low-risk substances (e.g. substances of natural origin). The risk assessment for groundwater should be redefined, including the metabolism of substances taken into consideration. An exposure model of feed additives in aquaculture should be included in the guidance. The use of *in silico* (computer simulated) methods should be reviewed and additional guidance on deriving data from such methods should be provided. Guidance on required ecotoxicological tests should be revised with additional information.

2. **Safety (Tolerance)**

   Three guidance documents will be updated concerning Target Animal Safety (TAS), consumer safety and user safety.

   For TAS, a trend has been set to derive data from laboratory animal studies, but the FEEDAP panel has questioned if the endpoints measured are the most appropriate for this purpose, and therefore whether this trend should continue. Statistical equivalence, rather than difference, should also be used for toleration evaluation as it's more consistent with statistical hypotheses posed.

   Historically, toxicological studies have been required for microbial products due to concerns over secondary metabolites produced during fermentation. However, with purification steps removing low molecular weight products, it was questioned whether such studies are required.

3. **Efficacy**

   It is possible that the current single efficacy and tolerance guideline will be split into two, as tolerance studies mostly involve *in vivo* studies for feed additives, whereas efficacy studies involve both *in vitro* and *in vivo* (with the exception of technological products for which *in vitro* only tends to be sufficient).

Professor Jurgen Gropp, also a member of the FEEDAP panel, presented a session at the meeting on 'Target Species and Efficacy: Options for Change'. Prof. Gropp started by saying that assessment of efficacy is based on "weight of evidence". Currently a minimum of three studies is considered core for each species and category of species indicated and for each effect claimed. An exception to this is nutritional additives where only one study in one animal species is required (it was proposed that a nutritional/digestive argument on paper could be used for other indicated species). It is currently considered that if efficacy is demonstrated in three major species, this is accepted to cover all species. The EC and Concerned Member States (CMSs) are to redefine major and minor species for the appraisal of feed additives. EFSA has suggested that the major species category covers only chickens for fattening, piglets and dairy cows (turkey and sheep, currently on the list, should be removed). Extrapolation of data from major to minor species is currently permissible if justified. However, moving forward, EFSA would like it to be restricted to the same "functional family" e.g. growth, reproduction etc.

It will be considered if the guidance documents (and indeed regulation 429/2008[2]) can be updated to better prescribe endpoints (a non-exhaustive list). For example, end-points for the assessment of efficacy of different functional groups of 'technological' feed additives are currently provided in Annex III to regulation 429/2008, and repeated in the dedicated FEEDAP panel guidance document. Expansion and better definition of this list was proposed, including, for example, suggested analytical methods used when generating the necessary data.

Pharmacodynamic (PD) data (mode of action) is welcome in the provision of efficacy data, however, the FEEDAP panel stressed that it cannot replace actual efficacy studies. Industry representatives responded at the meeting to say that PD data would assist in the reduction of the number of studies required. Considering that the '3Rs' objective in the EU is to Replace, Reduce and Refine the number of animals used in studies/testing, this has the potential to support that objective.

When considering the standard of compliance for safety (and efficacy) studies for feed additives, currently non-GLP studies are accepted, provided demonstration of control is shown (the compliance with GLP is only a suggestion in the present guidance documents and regulation). It is seriously being considered whether to implement a "must" for GLP compliance in the regulation and guidelines update.

Different working groups will be established for revision of the guidance documents. EFSA indicated that a timeline for guidance revision would be published in Q3 2016, but again there has been no further news on this at the time of this article going to print.

Presentations made by FEEDAP panel members at the EFSA meeting with stakeholders tended to pose questions for ideas for change, rather than state what the intentions for revisions are. Ultimately, the FEEDAP panel would like stakeholder involvement in the changes to be made to the guidance documents. An EFSA action is to organise a one day tripartite meeting (EFSA, EC and stakeholders) to discuss proposed changes to efficacy requirements, initially. EC agreement to this would be required first.

The FEEDAP panel believes that revision of the guidance documents should take place now, rather than waiting for the regulation update; otherwise it would mean at least a four year delay. Industry appeared to disagree at the meeting; feeding back that the regulation update should come before revision of the guidance documents.

Conclusion

The EFSA meeting with stakeholders on feed additive applications provided a valuable face to face opportunity to learn of the intentions of the EC and FEEDAP panel regarding proposals to amend Regulation no. 429/2008[2] and the associated guidance documents. Timelines for adoption of the proposed updates should become better defined, but clearly a great deal is up for discussion between the EC, EFSA and stakeholders.

References

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. Available at: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32003R1831&from=EN (accessed 09 October 2016).
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. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:133:0001:0065:EN:PDF (accessed 09 October 2016).
3. Animal Nutrition Section of The Standing Committee on Plants, Animals, Food and Feed (PAFF Committee) - Agendas and Meeting Summary Reports. Available at: http://ec.europa.eu/food/animals/committees/sc_animal-nutrition/index_en.htm (accessed 09 October 2016).