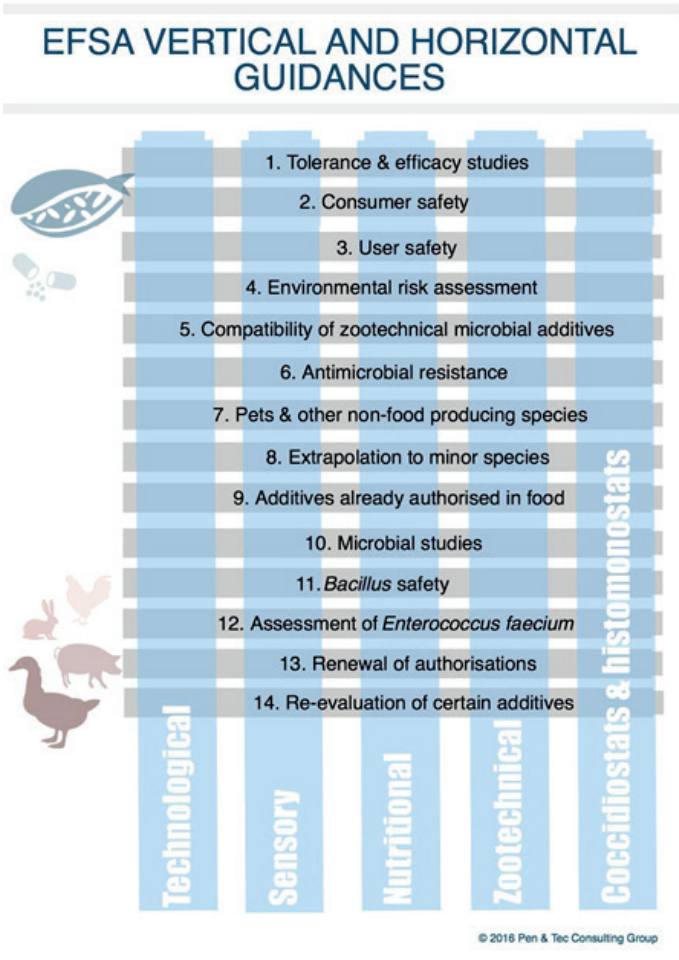
Update on EFSA FEEDAP Guidance Documents – *What are the Potential Benefits?*

PEER REVIEWED

On 14 -15 July 2016, EFSA held a meeting to present and collect feedback from stakeholders on the proposed changes to the FEEDAP technical guidance documents, which are intended to assist applicants in the preparation of technical dossiers for the authorisation of additives for use in animal nutrition. The aim of the meeting was to create a platform to exchange views on scientific issues related to the preparation and the risk assessment of applications for the market authorisation of feed additives with EFSA stakeholders. The full proceedings and presentations can be accessed via the EFSA webpage (www.efsa.europa.eu).

Why are EFSA Updating the Guidance Documents?

Currently, there are five 'vertical' documents, one for each feed additive category, and 14 'horizontal' documents, each dealing with specific aspects relevant to one or more additive category (e.g. tolerance and efficacy studies, microbial studies, etc.).



Whilst many of these guidance documents have been updated over the years, EFSA recently performed an analysis to identify which existing guidance documents were in need of a technical update (EFSA, 2016), and to assess whether or not the current guidance is fit for purpose. The principal drivers behind the need for revised guidance were:

- Parts of the existing guidance documents were developed before the re-evaluation and/or before the submission of actual dossiers (e.g. most technological and sensory additives) with requirements that are no longer relevant or appropriate
- Changes in EU farming practices
- Advances in technology and knowledge
- Development of new methodologies and improvements in conducting and reporting studies
- New/novel categories are not covered (e.g. nanoparticles)
- Modification/harmonisation of assessment methodologies from within EFSA and other European scientific bodies (e.g. OECD, ECHA, EMA).

What are the Benefits to Industry?

- Consolidated guidance will be more user-friendly and easier to interpret and apply
- Clearer guidance will enhance the quality of the dossier, which may reduce the likelihood of a negative opinion
- Updated guidance will better reflect advances in knowledge (e.g. better statistical approaches), technology (e.g. advanced molecular techniques) and common practices (e.g. current EU farming practices)
- Reduction of animal studies contributes to the 3Rs and saves money on expensive in vivo studies
- Harmonisation between other EFSA panels and other European scientific bodies allows for more robust applications
- The addition of novel categories (e.g. nanoparticles) allows applicants to build a robust body of evidence to support safety in the target species, user, consumer and environment

What are the Proposed Changes?

EFSA FEEDAP Panel members presented the proposals for change that are currently under consideration. General proposals included removing the current five 'vertical' guidance documents and introducing one guidance document covering Section II (characterisation of additives) or to consolidate the existing five or six guidance documents relating to microbial products. They also proposed splitting the current technical guidance on tolerance and efficacy in target animals. More specific changes were also discussed, which included:

Guidance on Environmental Risk Assessment
EFSA have identified this guidance as a priority as it requires a technical update and furthermore, it is not consistent with other approaches used within EFSA and other European scientific bodies. The main issues identified were:

1. The need to harmonise approaches with other frameworks that consider the environmental impact of chemicals (e.g. REACH)
2. Protection goals should be clearly defined: What ecosystems and communities are we aiming to protect?
3. Phase I should be revised. The decision tree should distinguish between high-risk (e.g. coccidiostats, heavy metals) and low-risk substances (e.g. naturally occurring substances)

Updated guidance will help applicants to clearly understand which environmental studies are required, based on the type of substance they have.

Non Holder-specific Authorisations
EFSA raised the question "what should the data requirements be for additives not linked to a holder-specific authorisation?"

In the absence of a specific formulation, is it necessary to collect data on:

- Potential contaminants?
- Physical properties (e.g. bulk size, particle size/ dusting potential)?
- Data on user safety other than any potential for systemic toxicity?

Clearer guidance on data requirements for non-holder-specific authorisations could potentially save time and money in conducting unnecessary studies.

Microbial Products
The representatives of the EFSA FEEDAP discussed the changes that are currently being considered. They highlighted that there is a need for a consistent approach between GMMs and non-GMMs, and a need to assess the relevance of toxicological studies for fermentation products from known-lineage micro-organisms. In addition, EFSA is collecting information on bacterial species (ongoing procurement) to check if there is enough scientific evidence to support the safe-strain lineage concept. Susceptibility testing is currently being revised (EFSA is revisiting the list of antibiotics to be tested, updating cut-off values, inclusion of new species, etc.). They added that the most common cause of inconclusive/negative EFSA opinions are related to genetic modifications. EFSA is also considering new assessment criteria based on experience, and plans to harmonise guidance among panels (FEEDAP, CEF) in the new guidance document for GMM fermentation products.

A consistent approach between GMMs and non-GMMs, and clearer guidance on microbial products will reduce the likelihood of a negative EFSA opinion.

Target Animal Safety and Efficacy Studies
A member of the FEEDAP Panel, introduced the potential options for change to target animal safety and efficacy studies, which included:

- Wherever possible, end-points should be clearly documented in order to provide transparency and predictability (e.g. if the number of species will be reduced, end-points will be different)
- Maintain a minimum number of "positive" studies where efficacy is demonstrated. Feed and water administration will still be considered bioequivalent in efficacy studies
- FEEDAP panel accepts target animal safety study durations of 35 days for piglets, and is discussing if also applicable for efficacy studies
- Consider replacing the 'major species' with broilers, piglets and dairy cows
- Extrapolation from minor to major species needs to be reviewed
- Studies on the mode of action are welcomed as supportive evidence, but efficacy studies will still be considered necessary
- Coccidiostats: Anticoccidial sensitivity tests (short-term) are preferred in poultry and can be a substitute for field studies. EFSA propose the option for only one field study

Updated guidance will allow the client to perform the minimum number of safety and efficacy studies in the target species, using clearly defined end-points, study designs and statistical analyses to ensure robust studies that reflect current EU farming practices.

What do EFSA Stakeholders Want to See?
After each EFSA presentation, representatives from FEFANA & AMFEP were given the opportunity to present their views. Following the formal presentations, the floor was then open for general discussion. The issues raised, and the proposals put forward by FEFANA and other EFSA stakeholders, were largely in agreement with those identified and proposed by EFSA. Overall, FEFANA said that they would like to see:

- Active substances
  - Establish a consistent concept in the guidelines to reduce misinterpretation
  - Ability to discuss unclear cases prior to application
- Identity and characterisation
  - Specifications/purity of the product with maximum levels of impurities defined based on the nature and safety of the additive
- Improve guidance on methods and thresholds for AMR marker genes and toxins
- Exemption of toxicology studies using a QPS approach
- FEFANA welcomes that EFSA has announced a Self-Task to develop a guidance document for the risk assessment of additives produced with GMMs, since new technologies have emerged and experience has been gained
- Efficacy trials and end-points
  - Guidance documents to provide protocols for testing end-points. Clarification of end-points for the different functional groups is welcomed
  - Possibility of tri-partite pre-submission meetings
  - FEFANA welcomes reconsideration of the value of meta-analysis (need for guidance)

  - Transparency in the acceptance and rejection of studies/scientific evidence during assessment
- Consistency in the assessment of fermentation products
  - Follow the Safe-Strain Lineage concept (Pariza and Johnson, 2001)
- Reduction in the number of animals used for safety evaluations
  - Avoid increasing the number of species groups while still leaving the option for niche markets
- Target species categories based on:
  - Physiological stage (growing vs. reproduction)
  - Digestive systems (ruminants, monogastrics, fish, etc.)
  - Metabolism (ovine vs. other ruminants)
  - Allow extended extrapolation of efficacy and safety studies across animal categories
- User safety
  - Consider alignment with harmonised CLP classification
  - Transparency and consistency of the use of physical characteristics for the assessment
  - User exposure is dependent on handling conditions which are outside the applicant's control
  - End-points for risk assessment: determine hazardous properties of the additive and determine which require risk management
- More involvement from stakeholders
- Consistency throughout the application process

During the general discussions, there was a request to apply a transition period for the new guidance documents. EFSA were also asked if stakeholders would be consulted as experts. EFSA confirmed that there will be a transitional period, and input from stakeholders will be sought. With regard to FEFANA's proposal for tri-partite pre-submission meetings to discuss unclear applications prior to submission, EFSA said that pre-submission advice is not planned to be offered.

Other comments raised at the meeting included:

- Good studies are often rejected due to minor issues and because current agricultural practices are not considered in the current guidelines. It was proposed that EFSA should use a 'weight of evidence approach' used, for example, by the European Chemicals Agency (ECHA)
- EFSA/EC should consider reduction of animal studies. EFSA are in favour of reducing animal studies, but they stress the requirement for well-designed studies. EFSA encourages the use of *in vitro* studies but stresses the need for thorough validation
- There was a request to delete the requirement to submit unnecessary chemical data (pKa, bulk density, etc.). EFSA agreed on this point
- Copyright issues with articles provided for literature searches: EFSA consulted the legal department, and they confirmed that a regulatory body is an 'exception' to the copyright legislation. However, EFSA cannot oblige applicants to provide a copy of the articles used in literature searches. If applicants cannot provide copies, EFSA will (although due to a lack of resource, this may have an impact on the process)

Next Steps

The EFSA FEEDAP Panel have prioritised updating the guidance on environmental risk assessment, and a specific working group has been established for this purpose.

Next, they will give priority to updating guidance for safety for target animals, the consumer and the user, followed by guidance on efficacy studies. In parallel, they aim to review and establish the data necessary for the characterisation of the additive. The remaining guidance documents will be reviewed subsequently, either by the existing working group, or by specific ad hoc groups as appropriate. The FEEDAP Panel will continue to engage with their stakeholders during the early stages of the guidance revision and aim to have draft versions of certain guidance documents available for public consultation in spring 2017. Pen & Tec will track the developments and will be able to help applicants with any questions or doubts concerning the registration process.

References

1. EFSA, 2016. Analysis of the need for an update of the guidance documents. EFSA Journal;14(5):4473.
2. Pariza & Johnson, 2001. Evaluating the safety of microbial enzyme preparations used in food processing: update for a new century. Regulatory Toxicology and Pharmacology. 33(2):173-186.

Abbreviations

AMR	Antimicrobial Resistance
CEF	EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
ECHA	European Chemicals Agency
EMA	European Medicines Agency
FEEDAP	EFSA Panel on Additives and Products or Substances used in Animal Feed
FEFANA	The EU association of Speciality Feed Ingredients and their Mixtures
GMM	Genetically Modified Micro-organism
OECD	Organisation for Economic Co-operation and Development
QPS	Qualified Presumption of Safety
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals

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