An Update on EFSA's New Guidance Documents for Feed Additives

On 17 October 2017, the EFSA FEEDAP Panel published three new guidance documents to help applicants with the preparation of feed additive submissions:

- *Guidance on the identity, characterisation and conditions of use of feed additives*
- *Guidance on the assessment of safety of feed additives for the consumer*
- *Guidance on the assessment of the safety of feed additives for the target species*

These guidance documents were adopted during the last FEEDAP plenary meeting in September 2017 and will enter into force on 1 May 2018. EFSA is also working on updating a fourth guidance (*Guidance on the characterisation of microorganisms used as feed additives or as production organisms*), expected to be adopted during the next FEEDAP meeting.

Draft guidance documents on the assessment of the safety of feed additives for the environment and guidance on the assessment of the efficacy of feed additives are being developed and are on the agenda to be discussed at the next FEEDAP meeting.

Prior to the adoption of the three new guidance documents, draft versions were made available for public consultation, whereby interested parties could comment & provide feedback. Pen & Tec submitted feedback on all three documents and some of the key changes proposed by Pen & Tec are discussed below.

Guidance on the Identity, Characterisation and Conditions of Use of Feed Additives

This new guidance will substitute feed additive category guidance documents currently in use (for technological, sensory, nutritional, zootechnical additives and coccio-diostats and histomonostats). In order to make the application procedure more efficient, Pen & Tec suggested that information and data requirements could be more concise. For example, giving a simple generic description of the production process, with key steps of feed additive manufacture, instead of the "detailed description" required by the guidance. Also, a shorter study duration to assess the stability in water (12 or 24h instead of 48h), depending on the practical use of the additive and quality of the water; or the possibility of using one single batch or pilot batches, when testing concentration of newly-produced feed additives for which five different commercial lots are not available (measuring intra-batch variability instead of batch-to-batch variability).

Pen & Tec also advised to specify the "feed dilution technique" as a possibility for analysing the active substance in premixtures. It is already accepted by the EURL and it only requires the premixtures to be adequately diluted and then analysed for the active substance with the same analytical method used for feed, so that no extra method validation/verification process is needed. EFSA has taken all of these comments into consideration and addressed them in the recently published Identity Technical Report.

Guidance on the Assessment of Safety of Feed Additives for the Consumer

The aim of this guidance is to reduce the use of laboratory animals in oral toxicity studies for microorganisms and production strains, replacing them by *in vitro* safety studies and analysis using modern genomic techniques (WGS, bioinformatic analysis, and phenotypic testing). In addition, reduced safety study packages were suggested for genetically modified strains whose parent strains were already proven safe (provided that genetic modifications do not raise additional safety issues), and to active substances and their combinations previously evaluated in the EU, or other geographic areas with well-established regulatory frameworks (e.g. USA). Methodologies for dietary exposure assessments that reduce the use of experimental animals should also be taken into account, especially if there is a long-term exposure risk, but only via infrequent food consumption.

Pen & Tec also pointed out the need for more harmonised approaches to gather consumption data, following standard methods and recognised by other agencies (EMA, US FDA, etc.). This would help avoid discrepancies in safety assessments and in the determination of maximum residue levels (MRLs). Moreover, consistency between the approach used in this guidance to determine MRL values, and other accepted models such as EFSA's pesticide residue intake, and JECFA model for veterinary residues, would prevent overly conservative exposure estimates. All comments, together with the reply from EFSA, are listed in the Consumer Safety Technical Report.

Guidance on the Assessment of the Safety of Feed Additives for the Target Species

This guidance document will replace the current EFSA technical guidance on tolerance and efficacy studies in target animals. The scope of the new guidance covers the assessment of safety in target species. A separate guidance will be developed for efficacy.

The main changes made to this guidance document were as follows:

As a first step in demonstrating the safety of a feed additive, the guidance proposes conducting an extensive literature search. The guidance says that the literature search should be conducted in a structured manner and cover at least the last 20 years. The references should be compiled using appropriate reference management software provided in .RIS format and copies of all relevant papers should be provided. This is a positive step, as if sufficient evidence can be found to support the safety of a product, then in vivo studies may not be required. Not only will this approach save the applicant time and money, it is also a positive step towards the "3Rs" (reduce, refine and replace the use of animals in science).

For **all additives** (except microorganisms), safety for target animals can be derived from suitable toxicological

studies with oral administration in laboratory animals. This means that expensive in vivo target animal safety (TAS) studies may not be required. When in vivo target animal safety studies are required, the number of trials needed will depend on the target species for which the application is made. For example, data from broilers can be extrapolated to turkeys. If the application covers all pigs and poultry, the requirement is limited to a total of three studies. Again, this approach will potentially save many companies time and money, while following the "3Rs" approach (reduce, refine, replace in vivo animal studies).

Study Design and Reporting

The new guidance says that TAS trials, when required, "should be compliant with the criteria established by a recognised, externally audited, quality assurance scheme (e.g. Good Laboratory Practice)". Currently, such a quality assurance scheme is recommended but it looks like it may become compulsory for all contract research organisations/labs after the new guidance is implemented. Good Laboratory Practice (GLP) studies are more stringent in the way in which study data are collected, audited and reported, which makes them more expensive, so this could have an impact on an applicant's budget. However, EFSA clarified that GLP is not mandatory, though trials should comply with the guidance and should be conducted at contract research organisations that have an in-house quality assurance team and are externally audited.

EFSA are becoming stricter on study design and statistical requirements. For example; the guidance asks that the rationale for the selection of the number of animals/replicates used (sample size calculation) is provided along with a power analysis. Whilst in practice this should always be done, it is not always reported. The guidance also requires that the protocol and any amendments/deviations be reported in the final study report. To date, EFSA have not required this information. This type of reporting is more in line with the requirements of GLP or Good Clinical Practice.

EFSA define the experimental unit as the smallest entity to which a treatment is applied. As such, if all animals in a pen share the same feed source, the pen is the statistical unit for all parameters. Pen & Tec proposed that when animals are weighed and sampled individually, then those individual data may be considered as individual replicates for statistical purposes. The only parameters for which the pen is the only possible statistical unit would be feed intake and feed gain. In the OECD/GLP guidelines, all other parameters (e.g. body weight, clinical signs, haematology, blood and urine biochemistry, organ weights, pathology, etc.) are considered as individual values. In relation to the use of a randomised block design, Pen & Tec suggested that flexibility be considered for certain cases where control animals need to be housed separately from treated animals (e.g. coccidiostat studies). EFSA responded by pointing out that guidance allows applicants to use other study designs where appropriate, as long as the approach is justified. In addition, Pen & Tec commented that innovation is driving new uses of feeds and feed additives (e.g. the use of feed additives in nutrients delivered from 18 days *in ovo* and in the period through hatching, delivery of chicks to farms, and acclimatisation of chicks at farms), therefore, EFSA safety (and efficacy) guidance documents may need to be adapted further as these innovations are taken into account, or become common industry practices.

Guidance on the Characterisation of Microorganisms Used as Feed Additives or as Productions Organisms

This guidance is expected to replace several EFSA guidance documents related to the same subject (e.g. Compatibility of zootechnical microbial additives with other additives showing antimicrobial activity, Microbial Studies, Assessment of bacterial susceptibility to antimicrobials of human and veterinary importance, *Bacillus spp.* safety, *Enterococcus faecium* safety). An important modification to be introduced is the requirement of using whole genome sequence analysis (WGS) for the characterisation of bacterial and yeast strains, as well as for the search of antimicrobial resistance (AMR). Consequently, Pen & Tec asked EFSA to specify its preferred databases for comparison of commonly used sequences, and its preferred method for taxonomic identification (e.g. 16S rRNA gene or house-keeping genes). At the same time, Pen & Tec suggested replacing the full WGS analysis request by a step-wise approach, where a previous investigation of minimum inhibitory concentrations (MICs) would determine the need of a WGS analysis (only if MIC > cut-off value for one or more antimicrobials, further investigation *via* WGS to determine the nature of the resistance would be required). EFSA has also been asked to indicate in the guidance if there are sufficient grounds not to provide the WGS. EFSA expects to discuss these comments and possibly adopt the guidance during the next FEEDAP meeting.

Pen & Tec's input on the guidance documents support the use of the "3Rs" for animal welfare. We are also in favour of adopting a pragmatic and more universal approach to data collection in order to keep the application process within reasonable time frames, maintaining the quality of the data provided for EFSA assessment, and rationally conveying information sources and procedures accepted by other important feed regulatory bodies worldwide.

Dr Hannah Lester

A research scientist with over 10 years' experience in running veterinary clinical trials for regulatory approval. She has a PhD in parasite epidemiology and an MSc in Veterinary Public Health. Hannah has managed Contract Research Organisations in the UK, and has also worked for government, providing veterinary policy advice.

Email: hannah@pentec-consulting.eu

Rocío Duchén Bocángel

An analytical chemist. She holds a Degree in Chemistry and a Master Degree in Forensic Chemistry, as well as a Master Degree in Translation Studies (scientific/technical translation from English to Spanish). Rocío has worked in research and has also collaborated as a specialist consultant in the food industry.

Email: rocio@pentec-consulting.eu