# Feed additive applications: Requirements and recommendations

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## Introduction and scope

In order to aid applicants in the preparation of Feed Additive dossiers and to aid FSA/FSS officials in carrying out dossier assessments, the FSA/FSS requested the Advisory Committee on Animal Feedingstuffs (ACAF) to provide advice on the key requirements and common application shortcomings for complying with the FSA/FSS regulated products application guidance and current scientific standards.

This information is based on the experience of dossier evaluation since 2021, by the ACAF, its predecessor Animal Feed and Feed Additive Joint Expert Group (AFFAJEG), and the FSA and FSS.

This document is not a replacement for the FSA/FSS scientific guidance requirements for the preparation of feed additive dossiers, and therefore those guidance documents should still be closely followed. The FSA/FSS may request information beyond the list presented below, depending on the particularities of the additive under evaluation.

Instead, these recommendations expand upon the FSA/FSS scientific guidance, showing the FSA/FSS's interpretation of its principles and reinforcing those existing requirements that allow for a full assessment which dossiers often fail to meet.

Please ensure that all the following are complied with:

## 1. Overall dossier

1. The version of the dossier that is submitted should be the most recent version, specifically intended to address the current application, rather than a previous application or an application for another type of authorisation or condition of use. In cases where additional information is submitted, (for example, previously addressed EFSA queries), it should be made clear to risk assessors what information is current and what is obsolete. When this additional information is submitted through multiple documents, it is asked that the applicant provides a consolidated version of the dossier, ideally using colour-coding of the text to clearly differentiate between new revision, current text, and obsolete.

2. The main sections of the dossier need not be subdivided into separate documents (e.g., Section II divided into 2.1, 2.2, etc.). We are aware that EFSA has requested for these

subsections to be individual PDF documents in their administrative guidance. However, FSA/FSS risk assessors and ACAF find that the traditional organisation of PDFs for Sections I, II, III, IV and V are easier to manage and help streamline the assessment process.

## 2. Section II - Identity and characterisation

3. Tests should be carried out on the final form of the additive and/or its ingredients, where relevant. For tests for which a different proxy-substance is used, evidence of equivalence with the active substance under evaluation will be required. In all instances in which the test was carried out on a product other than the final form of the additive, this should be explicitly stated and the justification for the use of the proxy set out in detail.

4. All information should be current and valid, including composition testing, impurity testing, certificates of analysis, certificates of compliance, etc. If certification or test results do not fall within the periods prescribed in FSA/FSS guidance prior to submission, they will not be considered valid.

5. Laboratory accreditation should be provided for all tests carried out.

6. Testing for all relevant impurities as specified in the guidance documents should be presented from the specified number of batches or grams of product, as required.

- a. When required to test for microbial contamination, in addition to the standard minimum microbiological contaminants tested for, please ensure that when the products contain or are produced by a species within the genus Bacillus, then Bacillus cereus is also tested in the final form of the product.
- b. The limits of detection (LOD) and quantification (LOQ) of the analytical methods should be given.
- c. For chemically-synthesised additives, please ensure that the final form of the product is tested to show absence of any substances used at any point throughout the production process. This is to ensure that residue levels of solvent and raw materials are within acceptable limits.

7. Whole Genome Sequence (WGS) is required for bacterial and yeast strains intended for use either as products or production strains. WGS is also recommended for filamentous fungi. WGS is required to confirm:

- a. Species identification.
- b. The absence of any potentially functional AMR genes or antimicrobial substance production genes.
- c. If these genes are present, further phenotypic investigations should be done to evaluate whether the genes are active and, for AMR genes, if they are present on plasmids or other mobile elements.
- d. The absence of any potentially functional toxic/harmful substance (e.g., toxins and virulence factors) production genes.

8. The applicant should use modern and contemporary bioinformatic tools to prove beyond reasonable doubt that the organism is safe and what it is claimed to be. The methodology chosen should ensure that the analysis undertaken on the WGS of the strain is sufficient to characterise the elements specified in paragraph 7.a-d, and described in sufficient detail to allow for its educated assessment. This should be presented in the form of a detailed WGS analysis document. If an inadequate method or bioinformatic package is selected and the applicant is not able to provide a new WGS analysis in time, the application may not progress to the assessment stage.

9. For fermentation products, (not containing microorganisms as active agents), the extent to which spent growth medium is incorporated into the final product should be indicated. For products consisting of or produced by Gram-negative bacteria, levels of lipopolysaccharides (LPS) should be analysed in the final product

10. The evaluation of the absence of DNA from the production strain should be quantitative. The smallest AMR gene should be targeted to provide evidence that DNA from an AMR carrying production strain is absent in the final product.

11. Dusting potential should be analysed using the Stauber-Heubach method, and the result given in mg/m3. Other methods and measuring units will not be accepted as evidence of dusting potential.

12. Particle size distribution should be analysed using laser diffraction.

13. Current and valid MSDSs should be provided in English language for all ingredients used in the production process, and these should comply with current UK legislation.

14. A full description of the manufacturing process should be given, including flow diagrams. The applicant should describe which impurities are monitored on a routine basis, the frequency of testing and the action limits set for each monitored impurity.

15. Current and valid quality assurance certificates and feed hygiene registration (where applicable) for all manufacturing plants, the applicant and the organisation supplying the additive in the UK should be given. For manufacturers outside the EU and UK, the applicant should provide evidence that the additive is manufactured in compliance with the Assimilated Regulation (EC) 183/2005 laying down requirements for feed hygiene.

16. As part of the application, a full HACCP protocol of the manufacturing process should be given, and the critical control points fully described.

17. In applications for coccidiostats and histomonostats, please ensure that all potential interactions with other coccidiostats, histomonostats or medicines are fully described, where applicable.

18. Stability and homogeneity tests should be carried out on the number of batches and feeds prescribed by the guidance and for all forms of the additive and addition methods.

- a. Applicants are encouraged to consider relevant UK conditions for the feed type and species under consideration when designing stability tests. As an example, in poultry breeder feed, a Salmonella kill-step is routinely applied requiring stability at 86oC for 2-6 minutes to be considered.

19. Stability in processing (pelleting/extrusion) should include details of the processing temperature, and the time for which the additive is exposed to this temperature. (This does not apply if the additive is intended to be added as a liquid post-pelleting).

20. Stability data should be provided for all forms or methods by which the additive can be added to feed, premixes or water. Stability conclusions from the tests should be included in the proposed label text, including processing temperature and retention time.

21. Stability in water, for additives intended to be distributed via water for drinking, should take into consideration the presence of excipients that could trigger growth of contaminating microorganisms.

22. Homogeneity should be evaluated in a minimum of 10 samples through testing, detailing the mixing operation used for the trial, including batch size, mixing time, formula used and which

section of the batch was sampled. If any samples are discarded or parts of the batch not sampled, a rationale should be provided. Written statements will not be accepted as evidence for homogeneity in substitution of test results. The coefficient of variation should be calculated for each homogeneity test.

23. The full proposed label text should be given, as well as the most current MSDS for the final product. Please make sure that the label and MSDS recommendations reflect the conclusions of the safety assessment, particularly those referring to user/worker safety, exposure assessment and methods to limit exposure.

24. The proposed label text should include the processing stability of the additive as well as safety considerations for users/workers.

# 3. Section III - Safety

25. All relevant information should be provided, including:

- a. Full papers from the literature in accessible PDF format, when these are referenced.
- b. If any literature papers are referenced as a substitute for tolerance studies, they will only be considered to be relevant if the same active principle has been tested, at an equal or higher dose than the one proposed in the conditions of use, and in the same species.
- c. Full certificates of analysis for the test material used in all tolerance, toxicology and environmental tests.
- d. For toxicological studies, evidence of satisfactory quality and rigour (e.g. GLP compliance).
- e. For tolerance studies, when these have not been carried out to GLP standard, justification should be given as to why the information provided should be considered equally valid, including evidence of any quality systems and/ or auditing processes undertaken. This may not guarantee acceptance as evidence of the validity of the trial.
- f. Please ensure that the final form of the active substance or additive is used for all toxicology studies presented for safety for the target species, consumer and the environment, as described in guidance. Please note that, for safety for the user/worker, the final form of additive should be tested.
- g. If a proxy other than the final form of the active is used for any test, evidence of equivalence with the substance under evaluation will be required. If this equivalence is not provided, the application will not be considered valid for assessment.
- h. The source and quality of all other ingredients that compose the final form of the product should be described. Consideration should be given as to whether any of the ingredients should be considered for an evaluation of the safety for the species, consumers, users/workers or the environment, even if the active principle does not require one.

26. For renewals and modification of an existing authorisation, a comprehensive literature review should be provided and summarised to identify any potential causes for concern for the additive. The relevant papers identified should be provided in full in PDF form. If the active substance is unique to the manufacturer and no literature data are available, a literature review on a similar active substance should be provided. Evidence of equivalence between both substances to justify the use of the second as a proxy should be provided.

27. For safety for the consumer, whenever relevant, please ensure that the exposure assessment section is fully covered, and an exposure assessment carried out using EFSA’s FACE tool. Where UK consumption data is available, applicants are encouraged to use it.

28. For safety for the user/worker, if the relevant tests are not provided to evaluate inhalation toxicity, eye irritation, skin sensitisation and skin irritation, the assessment will conclude that the product should be considered potentially hazardous by the relevant route of exposure. Applicants

are encouraged to use in vitro tests for skin irritation, eye irritation and skin sensitisation studies. Please note that highly proteinaceous additives such as enzymes and microorganisms, will be regarded as potential respiratory sensitisers.

29. For safety for the user/worker, tests should be carried out on each formulation of the additive proposed by the applicant. If tests are not conducted on all formulations, a comprehensive rationale for extrapolation of results should be provided.

30. For safety for the environment, a Phase I assessment should be carried out to determine whether a Phase II assessment is required. In cases where a Phase I is not required, an extensive rationale for this omission should be provided.

# 4. Section IV - Efficacy

31. All relevant information should be provided for all studies, including:

- a. Full study reports and certificates of analysis for the product being tested, including recovery of the additive in feed/water.
- b. Detailed description of the study design providing a description and justification for the experimental unit and degree of replication.
- c. Compliance with internationally recognised quality assurance standards should be provided.
- d. Raw data in digital format, including all data points originally captured.
- e. Evidence of compliance with appropriate animal welfare regulations.
- f. Addressing any anomalies noted during the trials, as well as observed adverse effects or mortality.
- g. Data presented in the main application dossier document should align with the data demonstrated in the full study report.
- h. Possible explanation for any large variance in the data

32. When carrying out the trials, animals should be selected to ensure the results are representative of UK industry practice. Animals should be healthy, and their age and sex distributions should be relevant to evaluate the efficacy of the additive under conditions to which the additive will be applied in UK practice. Study design conditions as specified in guidance should be followed for the trials to be considered as part of the efficacy evidence package.

33. If literature studies are presented as part of the evidence package for efficacy, please ensure that the study design is relevant to the conditions of use of the additive as proposed in the request for authorisation.

34. Literature studies will only be considered to be relevant if efficacy was demonstrated using the same active principle, at an equal or lower dose than the one proposed in the conditions of use, and in the same species.

35. The relevant papers identified should be provided in full in PDF form.