EFSA Info Session on Applications - FEED
Technical Meeting with Stakeholders,
Session 2: FEEDAP Guidance Documents update: Selected Topics

TARGET SPECIES AND EFFICACY

OPTIONS FOR CHANGE

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OUTLINE

- **Why shall efficacy be assessed ?**
- **How is it currently assessed !**
- **Options for change ?**

WHY SHALL EFFICACY BE ASSESSED ?

Article 5 (2) of Regulation (EC) No 1831/2003

The feed additive shall

not be presented in a manner which may mislead the user

Regulation (EC) No 429/2008, Annex II

shall demonstrate the efficacy for each proposed use and satisfy at least one of the characteristics set out in Article 6 (1) of Regulation (EC) No 1831/2003,

WHICH ENDPOINTS ?

Article 5 (3) of Regulation (EC) No 1831/2003

The feed additive shall:

favourably affect the characteristics of feed,

favourably affect the characteristics of animal products,

favourably affect the colour of ornamental fish and birds,

satisfy the nutritional needs of animals,

favourably affect the environmental consequences of animal production,

favourably affect animal production, performance or welfare, particularly by affecting the gastro-intestinal flora or digestibility of feedingstuffs, or

have a coccidiostatic or histomonostatic effect.

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ADDITIVE CATEGORIES

The criticism of the FEEDAP Panel on the existing categories is known since a many years.

The categories are not consequently derived from Article 5 (3) of Regulation 1831/2003.

Adding more and more functional groups to this system would definitely not improve clarity and functionality of the system.

Does probably not support innovations

ADDITIVE CATEGORIES

- **The audience is well aware of it.**
- **No examples will be given.**

WHICH ENDPOINTS SHALL BE ASSESSED ?

AS A CONSEQUENCE

Option for a change

In Regulation (EC) No 429/2008, Annex II

shall demonstrate the efficacy for each proposed use and satisfy at least one of the characteristics set out in Article 5(3) of Regulation (EC) No 1831/2003

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EFFICACY TO BE ASSESSED

In addition - option

Attention shall also be paid to known or potential biological or physico-chemical interactions between the additive, other additives and/or veterinary medicines and/or components of the diet, where this is relevant to the efficacy of the additive concerned (e.g. compatibility of a microbial additive with coccidiostats and histomonostats or organic acids).

WHY FEEDAP PROPOSALS ?

Dual purpose of Regulation 429/2008

- **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**

- **The said regulation binds the applicant**

- **The said regulation binds (not fully) the assessor**

EFFICACY PRINCIPLES

ASSESSMENT – THE BASIS

- **Need to have a minimum level of evidence of efficacy. In this regard, efficacy assessment should be based on the effect claimed which results in a positive outcome for the animals, farmers or the environment.**
- **For this the minimum number of positive studies necessary which provides reasonable evidence of efficacy should be specified.**
- **Whenever possible, the end-points for the assessment should be documented in order to provide transparency and predictability to the assessment. However, an exhaustive list of end-points is not possible.**

EFFICACY PRINCIPLES

NUMBER OF STUDIES

- The core number is three studies
- For animal species/categories claimed
- For the effect claimed

Exemptions

- Nutritional additives: only one and only one animal species, if one. Food additives.
- If demonstrated for three major species, conclusion is made for all species
- Option: major replaced by chicken for fattening, piglets and dairy cow

EFFICACY PRINCIPLES

ASSESSMENT – THE BASIS

- The dossier shall include detailed reports of all the studies performed regardless of their outcome, presented in accordance with the numbering system proposed in this Annex.
- Why: The proposed addition is to ensure that all studies available to the applicant relating to the safety or efficacy of the additive should be submitted in the technical dossier, regardless of the outcome.

That allows judgement by Weight of Evidence

EFFICACY PRINCIPLES

ASSESSMENT – THE BASIS

- For studies with animals, oral administration of additives via feed or water delivering the same dose is, in principle, considered as bioequivalent.
- Studies, including those that have been conducted and published previously or coming from peer review, shall be performed and documented according to appropriate quality standards (e.g. Good Laboratory Practice (GLP)) in accordance with Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws,

GLP, an element of "refinement"

EFFICACY PRINCIPLES - EXCEPTIONS

Additives authorised in food

- **In principle there is no need for efficacy demonstration.**
- **For technological additives, there are exceptions due to differences between food and feed characteristics (e.g. for anticaking)**
- **For sensory additives, there are exceptions due to differences between food and feed characteristics (e.g. colorants)**

THE THREE Rs

The principles of **Replacement, Reduction and Refinement** were first proposed by Russell and Burch ('The Principles of Humane Experimental Techniques', 1959)

The use of RRR is triggered:

- By the responsibility of humans to the welfare of animals (*"humanest possible treatment of experimental animals"*)

The consequences are:

- **Replace and reduce use of animals, IF POSSIBLE**
- **Refine is a must (also for reduction)**
- **Reduction of budgets is not a correct interpretation**

ANIMAL SPECIES / CATEGORIES

Definitions - proposal

- **Minor to major**
- **Delete sheep (meat animals) and turkeys**
- **Pets and other non food-producing animals**
- **Delete horses**

EXTRAPOLATION FROM MAJOR TO MINOR SPECIES

Where the additive is already approved for a physiologically comparable major species for the same function and where the mode of action of the additive can be reasonably assumed to be the same, extrapolation of efficacy is accepted without further experimental evidence in the minor species.

- **If efficacy demonstration is required, the duration of efficacy studies shall be analogous to the comparable production stages of the physiologically comparable major species.**
- **Extrapolation will be in the same functional family (growth or reproduction)***

* **Does „laying" sufficiently describe reproduction ?**
* **What about fertility (breeders) ?**

EXTRAPOLATION FROM MAJOR TO MINOR SPECIES

Poultry:

Extension from chicken for fattening to chicken reared for laying

Extrapolation from chicken for fattening to all growing minor poultry

Extrapolation from laying hen to all minor laying poultry

?? Extrapolation to breeder hens ??

- **Can we extrapolate from dairy cows to lactating sheep or goat?**
- **The classification into major and minor species is not helpful for that purpose.**

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PETS AND OTHER NON FOOD-PRODUCING ANIMALS

The requirements for the different categories/functional group of additives apply

- For additives for which efficacy has been demonstrated in major species and provided that the effect claimed for the major species is the same, one *in vivo* study is required for each pet/non food-producing species to a maximum of three studies in total.
- Where the effect claimed in the pet/non food-producing species is not the same as that described for the major species three *in vivo* studies in one pet/non food-producing species are required. If the application is made for more than one pet/non food-producing species, a single additional study would be required for each additional target species up to a maximum of three species in total.
- For additives for which efficacy has not been demonstrated in major species the same principle as in 2) applies.

If three *in vivo* studies are required, at least one long-term study must be provided.

EFFICACY ASSESSMENT – EFFECTS CLAIMED

In vitro vs in vivo

Studies in FEED vs ANIMAL studies

For additives affecting the characteristics of feed, efficacy shall be demonstrated using a laboratory-based study

***In vivo* animal studies are required for all additives which exert the intended effect in the target species**

Present procedure – option of change ?

TECHNOLOGICALS – *IN VITRO*

Functional Group	End-points for demonstration of efficacy
(a) Preservatives	Inhibition of ~~microbial~~ **the** growth~~, particularly that~~ of biotic and spoilage **micro**organisms. The period for which a preserving effect is claimed shall be demonstrated-
(b) Antioxidants	Protection against oxidative damage of key nutrients/components during feedingstuff processing and/or storage. ~~The period for which a protecting effect is claimed shall be demonstrated.~~
(i) Anti-caking agents	Flow ability. ~~The period for which a protecting effect is claimed shall be demonstrated.~~
(j) Acidity regulators	pH and/or buffering capacity in feedingstuffs **and/or water**
(k) Silage additives	Improved production of silage (better preservation of nutrients); Inhibition of undesirable microorganisms; Reduction of effluents; Improved aerobic stability
(n) Hygiene conditions enhancers	**Reduction of a specific microbial contamination relevant to food safety**
Other technological additives	**The end-points used for assessing the functionality of the additive should b defined and justified.**

TECHNOLOGICALS – *IN VITRO* – MORE DETAILS ?

Functional Group	End-points for demonstration of efficacy
(g) Binders	Pellet durability or performance of pellet formation, **e.g. by relative motor load, pellet hardness (Kahl tester), pellet durability index, abrasion characteristics,**
(i) Anti-caking agents	Flow ability**, e.g. by Flow meter or Schulze ring shear tester**

TECHNOLOGICALS – *IN VIVO*

Functional Group	End-points for demonstration of efficacy
Substances for reduction of the contamination of feed by mycotoxins	**Reduced concentration of mycotoxins in food of animal origin;** **Reduction of the absorption of mycotoxins** **Increased excretion of mycotoxins** **Degradation of mycotoxins**

Annex III Technological additives should be changed - option

SENSORY – *IN VITRO*

(b) For substances that add or restore colour in feedingstuffs:

evidence of efficacy shall be provided by adequate laboratory studies reflecting the intended conditions of use in comparison with control feedingstuffs.

EFFICACY ASSESSMENT – EFFECTS CLAIMED

MODE OF ACTION

In principle welcomed as supportive evidence

***In vitro* – does not accurately enough predict the effect in the animal under farming conditions.**

Present procedure – option for change?

IN VIVO STUDIES

In vivo animal studies are foreseen for all additives which exert the intended effect in the target species. Generally, **zootechnical parameters** (e.g., growth, feed conversion, milk yield, laying performance, carcass composition, reproduction performance) can only be reliably measured in **long term efficacy studies**, whereas effects on **other parameters** (e.g., absorption, digestibility, excretion, retention) may be better demonstrated in **short term efficacy studies**.

The choice of short or long term studies or a combination of both will depend on the effect and/or mode of action of the additive.

In general, three studies showing a favourable response are the minimum number required to demonstrate efficacy for the relevant target species/categories.

SHORT TERM EFFICACY STUDIES

Short term studies can be used to assess/measure the bioavailability or bioequivalence of an additive, effects on the absorption and/or excretion of nutrients or other substances or palatability of feed.

Bioavailability is defined as absorption/transport of the active substance(s)/metabolite(s) to the target cells/tissue(s) where it exerts a typical function/effect.

Bioequivalence studies may be used to demonstrate the extent to which a novel form or source of a nutritional additive or additives (e.g. which colours food of animal origin) can substitute for an equivalent additive already approved or established.

SHORT TERM EFFICACY STUDIES

Digestibility can be measured as apparent or true, faecal or ileal digestibility. Balance studies are preferred because they deliver additional information on quantitative excretion and retention of a nutrient/energy.

Anticoccidial sensitivity tests are studies where poultry are artificially infected with field strains of *Eimeria* recently confirmed as pathogenic/resistant.

Other short term efficacy studies with animals may be proposed as appropriate (e.g. palatability studies).

SENSORY – COLOURING

(c) For substances which favourably affect the colour of ornamental fish and birds:

Studies demonstrating the effect(s) shall be performed on a representative range of target animals receiving the additive at the recommended levels of use. Colour changes shall be measured using the appropriate methodology. Evidence of efficacy may also be provided by other experimental studies (e.g. bioequivalence) or by reference to scientific literature.

DATA ARE REQUIRED

SENSORY – FLAVOURINGS

Where the function requested for feed is the same as that used in food, no further demonstration of efficacy might be necessary.

If the substance is not authorised in food evidence of the flavouring properties, usually on the basis of the published literature, shall be provided.

Otherwise animal studies may be required.

DATA ARE REQUIRED

NUTRITIONAL ADDITIVES

Efficacy studies are not required for urea, amino acids, amino acid salts and analogues already authorised as feed additives, compounds of trace elements already authorised as feed additives and vitamins, pro-vitamins and chemically well-defined substances having similar effect **already authorised as feed additives.**

Functional groups “amino acids” and “vitamins” require better definition !

NUTRITIONAL– *IN VIVO*

A short term study is required to support efficacy for urea derivatives, amino acid salts and analogues not already authorised as feed additives, compounds of trace elements not already authorised as feed additives and for vitamins, pro-vitamins and chemically well-defined substances having similar effect not already authorised as feed additives.

For vitamins, compounds of trace elements and some amino acids salts and analogues, a bioequivalence study could demonstrate efficacy. Generally, it will be sufficient to demonstrate efficacy in a single animal species or category including laboratory animals.

ZOOTECHNICAL ADDITIVES

(2) Additives favourably affecting the environmental consequences of animal production

For these additives which favourably affect the environment (e.g. reduced nitrogen or phosphorus excretion or reduced methane production, off-flavours), evidence of efficacy for the target species can be given **by three short term efficacy studies** showing significant beneficial effects. The studies shall take into consideration the possibility of an adaptive response to the additive.

LONG TERM EFFICACY STUDIES

Generally, the duration of efficacy trials shall correspond to the application period claimed. The minimum duration is stated in Annex IV.

If an additive is applied for a specific and shorter period than given by the animal category definition, or where a minimum duration is not specified in Annex IV, it shall be administered according to the proposed conditions of use. However, the observation period shall not be shorter than 28 days and shall involve the relevant end-points

ZOOTECHNICAL ADDITIVES

(1) Additives favourably affecting production and/or performance of animals in good health

The effects can only be demonstrated in relation to each target animal species or category. Depending on the properties of the additive, outcome measures may be based either on performance characteristics (e.g. feed efficiency, average daily gain), increased yield of animal products, herd performance or reproduction parameters.

For enzymes which affect the digestibility of non-starch polysaccharides (NSP), phytate phosphorus or protein, short-term (balance) studies can substitute for long-term studies provided that properly defined and specific methods are applied. All studies for demonstration of the efficacy of phytases can be designed as short-term studies. For other enzymes, two short-term studies could replace two long term studies.

ZOOTECHNICAL ADDITIVES

(3) Other zootechnical additives including those affecting animal welfare or the characteristics of food from animal origin

For other zootechnical additives, the requirements for efficacy studies should be determined on a case by case basis, depending on the nature of the substance and the effect intended.

The selection of the end-points should be properly justified.

COCCIDIOSTATS AND HISTOMONOSTATS

- These additives protect the animals from the results of an invasion of *Eimeria* spp. or *Histomonas meleagridis*. Importance shall be attached to evidence of the specific effects of the additive (e.g. species controlled) and its prophylactic properties (e.g. reduction in morbidity, mortality, oocyst excretion and lesion score).
- Information on the effect on growth and feed conversion (birds for fattening or reared for laying and rabbits) shall be provided, as appropriate.

COCCIDIOSTATS AND HISTOMONOSTATS

Experiments with artificial single and mixed infections (e.g. battery cages for poultry) are intended to demonstrate the relative effectiveness against the parasites and do not require replication.

Three significant results are required for studies simulating use conditions (e.g. floor pen studies with poultry, battery cage studies with rabbits).

Three field studies in which a degree of natural infection is present are also required. However, anticoccidial sensitivity tests (short term) are preferred in poultry and will substitute for field studies.

Option: Not more than one field study