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Guidance on the assessment of the efficacy of feed additives

EFSA meeting, 28 June 2023

Revision of the guidance document – industry proposal

- General comments
- Recommendations for the different categories of additives and/or functional groups
- Number of *in vivo* efficacy studies
- General requirements for the *in vivo* studies

General comments

- ✓ We appreciate EFSA´s initiative to update the guidance document and the opportunity to contribute to this process
- ✓ Our comments are complementary to the joint industry position from October 2021
- ✓ We expect that this exercise will serve to achieve a solid, future-proof set of principles and recommendations to help applicants designing their efficacy studies
- ✓ Keeping in mind that:
  - Recommendations shall not limit the access to safe, innovative products to the EU market
  - Efficacy of additives with benefits to the environment or animal welfare can be demonstrated outside of “classical zootechnical types of studies”

General comments – efficacy studies

- ✓ Industry asks for formal technical advices from EFSA-FEEDAP on efficacy studies to ensure study protocols are acceptable and to reduce “study rejections”
  - We expect clear guidance/recommendations, including agreement on the protocols and acceptable deviations from EFSA’s recommendations when it is not possible to follow due to constraints in research facilities
  - In line with the approach followed by the ECHA or the FDA in the US
  - Especially important for functional groups covering a broad range of products and functionalities (e.g., physological condition stabilisers)

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General comments – risk assessment process / efficacy

- ✓ EFSA is no longer getting back to applicants when experts consider submitted efficacy studies do not allow to conclude on the efficacy (e.g., three in vivo studies “rejected”) leading to non-conclusive opinions
  - It creates additional burden to applicants as well as, also for the EC and the MS, to manage the request of additional information as a post-opinion step, and to EFSA as a new mandate as to be handled
  - Longer period to get an authorization and reduced possibility to introduce new/innovative products on the EU market
  - Applicants should be allowed to provide new studies in the frame of the application (SIn request), as it was the case in the past

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General comments - opinions

- ✓ Need for transparent opinions as regards all submitted studies and their description:
  - In contrast to the past, studies not accepted/considered are not described in the opinion. That would be in line with other EU agencies (i.e., EMA)
  - It gives wrong impression to the SCOPAFF and to the public on dossier quality and ability of industry to prepare their submissions
  - Including all studies (and justifications for acceptance/rejection) is important for the risk management process
  - The fact that all studies are available thanks to the transparency is not sufficient as it is not feasible for SCOPAFF and EC to review all submitted data

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Recommendations for the different categories of additives and/or functional groups

Technological additives – Hygiene condition enhancers

For the sake of completeness, we repeat the recommendations made on 21 Nov 2021 on the assessment of efficacy of Hygiene condition enhancers, with the main recommendations below:

- Set of efficacy data to present the *potential* to be effective, not all possible scenarios, due to the wide variety of conditions in practice
- Suggestions for the design of studies, with the most important variables being moisture / Aw, and the use of regression as preferred statistical model
- Alternatives in the study design, depending on the practical situation (e.g., aerobic vs anaerobic, microorganism spiking vs. natural contaminations, order of administration of additive and MO)
- Arguments in favor of sterilization of feeds prior to inoculation
- Arguments against endpoints at a too high taxonomic level (e.g., 'yeasts')

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Zootechnical additives – functional groups

Digestibility enhancers/Enzymes

- The guidance requires demonstration of metabolizable energy for enzymes (i.e., polysaccharidases)
- Recent scientific knowledge supports the possibility to assess efficacy by measuring increased "**digestible energy in balance trials**"
- Several scientific references are supporting this option

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Zootechnical additives

Additives favourably affecting the environmental consequences of animal production

- Applications are required only for feed additives having a *primary effect* on the environment
- Many feed additives currently authorized in a different functional group play a significant role in mitigating the environmental impact of animal production through their *secondary effect*
    - e.g., digestibility enhancers or gut flora stabilisers, nutritional additives such as amino-acids;
- Those additives do not require application if claims are made within the scope of Article 13 of Reg. (EC) No 767/2009
- This aligns with the EC's proposal for the revision of Reg. (EC) No 1831/2003 (policy option 4c, introducing a claims system)

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Zootechnical additives

Additives favourably affecting the environmental consequences of animal production

- There is a need to foster innovation and incentivize applicants to submit applications for this functional group
- A reduction in the number of in vivo studies for assessing the direct environmental benefit of an additive would facilitate the process
  - ➢ Combination of *in vivo* (1 per major species/category) and *in vitro* studies

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Zootechnical additives

Physiological condition stabilisers (PCS)

- A substance (or micro-organisms) when added to feed, aiming at stabilizing the physiological conditions of animals in good health, in particular under conditions of stress inherent to the life cycle of an animal and typically occurring under animal husbandry conditions representative of the EU

- Stress factors such as social, nutritional, immune, oxidative, and environmental factors can weaken the defense mechanisms of healthy animals, making them more susceptible to disease
- The extent and timing of these stress factors' effects depend on the physiological conditions of the animal, encompassing species, categories, and life stages

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Zootechnical additives

Physiological condition stabilisers (PCS)

Endpoints/Parameters:

- Endpoints for PCS often differ from classical zootechnical performance parameters
- Claimed effect to be described by applicants as well as relevant (and measurable) endpoints and parameters to demonstrate the benefit(s) of the additive (justification required)
- Applicants would appreciate an open, non-exhaustive list of acceptable endpoints/parameters to assess the efficacy of PCS. Illustrative examples could be included to further help applicants (in the guidance or in a dedicated technical note)
- The updated guidance should ensure future-proofing, allowing for the introduction of innovative solutions that may not be currently foreseen

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Zootechnical additives

Physiological condition stabilisers

Required studies:

Inherent to the intended use, efficacy testing protocols should provide scientific evidence for the efficacy of a feed additive by:

Demonstration of mode of action (with *in vitro / ex vivo / in silico* studies)

- if suitable, validated systems are available
- reduction of unnecessary animal testing – 3R principle
- faster testing

AND/OR

***in vivo* studies**

- accurately reflect the intended use of the additive
- stress challenge models or studies conducted under moderate stress conditions can also provide insight into real-life animal situations
- Short-term studies, with durations linked to the measured endpoints,

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Coccidiostats and histomonostats

Efficacy studies in poultry (i)

In the current guidance sensitivity studies are preferred to actual field studies. Aspects to be considered:

i. Given mode of action - Veterinary Medicines Guideline principles should apply to the efficacy assessment of coccidiostats and histomonostats:
    - Field trials as per the claimed posology and treatment schedule provide the best guarantee that a product will effectively work under field conditions
        - against a placebo/blank with the negative control group kept as small as possible due to animal welfare reasons
    - Field trials can comply with EFSA requirements
        - Use according to label
        - Minimum duration of 28 days

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Coccidiostats and histomonostats

Efficacy studies in poultry (ii)

ii. The EFSA guidance now places emphasis on clinical endpoints (oocysts and lesion scores)

- Collecting and analysing secondary endpoints like body weight and feed intake can provide valuable insights into the overall efficacy of the product under field-like conditions and demonstrate the value of the additive for the farmers
- Endpoints, such as oocyst counts or lesion scores, may be challenging to obtain conclusive data from

iii. Number of studies: three ASTs (Anticoccidial Sensitivity test) and three floor pens:

- high number of animals to be challenged and slaughtered (battery cages not accepted in EU animal husbandry)
- the scientific benefits from conducting both an AST study and a floor pen study do not justify the use of additional animals
- **Proposal to reduce the number of animals used**
  - **field studies or pen studies (as they mimic closely the actual situation in the farms) for new application**
  - **AST or field data for renewal of authorisations**

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Coccidiostats and histomonostats

Efficacy studies in poultry (iii)

iv. The EFSA guidance on renewals – "*Evidence of the maintained susceptibility of recent (not older than 3 months at the time of study start) strains of Eimeria spp.*"

- Time limitation impossible to uphold as you need to time to characterize inoculum and perform virulence titration
- This time limitation should not be included in the efficacy guidance

v. Pen vs individual birds

- Only the pen serves as experimental unit → high number of birds needed to obtain statistical significance
- Using the individual bird as experimental unit for coccidiostats will be in line with 3R principles

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Coccidiostats and histomonostats

Efficacy studies in rabbits (i)

Field trials for rabbits are often not considered as acceptable by the EFSA-FEEDAP:

- even if recommended in the current EFSA guidance for coccidiostats
- not in line with the veterinary medicines' guideline

Request for significant differences in oocyst counts and lesion scores:

- no published guidance on how these efficacy trials in rabbits should be conducted – clarity on the protocols is needed
- no published scoring system for lesion score
- we suggest a harmonized lesions scoring system (successfully used in three different trials and foreseen for submission in a scientific publication soon)

As for poultry, a reduction in the number of studies is to be considered

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Number of *in vivo* efficacy studies

Number of efficacy studies in minor species

"The number of independent *in vivo* efficacy studies required depends on the number of target species/categories for which application is made." – Section 3 of the guidance

We propose to reduce the number of required in vivo studies to 1 in case of applications in a minor species and/or category

- This approach aligns with the principles of 3R in animal testing
- Encouraging industry to develop innovative solutions specifically tailored for species and/or categories that currently lack authorized zootechnical additives (e.g., rabbits, horses, insects).

Proposed modification of the guidance:

"In general, three studies are required per species/category unless the application is for a minor species and/or a minor category for which no data from a major species/category are available to extrapolate from. In this case, one *in vivo* study is considered sufficient."

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Table 4. Extrapolation of efficacy data from certain species to other physiologically related species

*Proposed amendments in **blue***

From	To physiologically related species
Chickens for fattening	other poultry for fattening (e.g. turkeys, ducks, geese, pheasants, quail, guinea fowl, ostrich) or categories (e.g. poultry reared for laying/breeding) and ornamental birds
Laying hens	other birds kept for egg production or breeding (e.g. turkeys ducks, geese, pheasants, quail, guinea fowl, ostrich)
Piglets(b) or pigs for fattening	other growing Suidae or categories (e.g. boars, guilts) at the corresponding developmental stage
Sows	other reproductive Suidae
Calves or cattle for fattening	other growing ruminant or camelids species (e.g. sheep, goat, buffalo) or categories (e.g. dairy heifers) at the corresponding developmental stage
Dairy cows	other dairy ruminants (e.g. goat, sheep, buffalo) and dairy camelids
Salmon or trout	ornamental fish
Horses	other Equidae
Rabbits	other Leporidae
Dogs	All Canidae
Cats	All Felidae
Any insect species	All insects

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Table 5. Minimum number of independent studies and target species required for the assessment of efficacy in applications covering multiple species/categories

*Proposed amendments in **blue***

Application for	Number of studies required and species
All growing ruminants (calves, cattle for fattening, sheep and goats for fattening, other minor growing ruminants, dairy heifers) and camelids	3 in calves 3 in cattle for fattening
All ruminants (calves, cattle for fattening, cows, sheep and goats for fattening and dairy production, other minor ruminants growing and reproductive) and camelids	3 in calves 3 in dairy cows
All ~~fin~~ fish (including ornamental fish)	3 in salmonids (salmon or trout) 1 in another fish species (this is proposed as other fish than salmonids are defined as minor species and as proposed in slide 17 we consider it as a refinement/reduction element to be taken into consideration for minor species)
Crustaceans	~~3~~ 1 in shrimp~~/~~ or in another crustacean species (minor species, 1 in vivo study)
Rabbits ~~(growing and reproductive)~~	~~3 covering both growing and reproductive animals~~ Rabbits are a minor species, we claim for simplification of that species description and to apply the same approach as for horses or pets, i.e. no category within the species unless specifically requested by the applicant
Pets (cats and dogs)	3 studies (unless efficacy has been demonstrated in a food-producing animal species and provided that the intended effect is the same. In that case, 1 study is sufficient)
Other pets	1 study
Horses	1 study
Rabbits	1 study
Insects	1 study

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Extrapolation from minor to certain major species

Currently, extrapolations from major species/categories of animals to minor species/categories are established and recognized

Possible extrapolation from minor species/categories to major species/categories:

- e.g., extrapolation from laying quails to all laying poultry or from dairy goats to all dairy ruminants
- In certain cases, conducting efficacy studies may be comparatively easier to ensure sufficient statistical power
- If a research facility possesses the necessary resources and capabilities, it can undertake such studies

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Duration of long-term efficacy studies – for minor species

"For minor species not included in the table above (i.e. Table 6), the duration of the studies should correspond to that of the physiologically related major species listed in Table 4 unless properly justified. For all other species/categories, the minimum duration should be 42 days for growing animals and 56 days for adult animals" – Section 4.2.2

- This recommendation is not suitable for species without major counterparts, such as horses, rabbits, insects, and/or snails.
- In the case of insects, a duration of 42 or 56 days is not appropriate due to their shorter lifespan and the potential for some species to have a larval stage as brief as one week
- We suggest that alternative durations, specifically short-term studies, could be proposed by the applicant if duly justified and if they enable reliable measurement of the proposed endpoint (text of the guidance could be amended to reflect this possibility)
- This is particularly relevant for feed additives in the functional group of "physiological condition stabilisers"

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Table 6. Minimum duration of long-term efficacy studies

Category	Definition of the animal category	Start	Minimum duration
Sows	Female animals having been inseminated/mated	Insemination/mating **Proposal for amendment/modification:** • For effects on reproduction: Insemination/mating • For effects on piglets, preferably at least 2 weeks before parturition until weaning	For effects on reproduction: two cycles (from insemination/ mating until weaning). For effects on piglets, preferably at least 2 weeks before parturition until weaning
Chickens for fattening	Birds raised for fattening	1 day of age	35 days 28 days if growth rate is ≥ 0.1 kg/day
Cows	Lactating cows	4~~–8~~ weeks after calving **Comments**: • Clarification on the rational for this recommendation would be appreciated • It strongly limits the number of research facilites where studies can be performed and significantly reduce the possibility of performing efficacy studies in dairy cows. • Additional information on these limitations could be provided to EFSA-FEEDAP **Proposal**: • Coming back to the initial recommendation of min. 4 weeks (2017 efficacy guidance)	84 days

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Table 6. Minimum duration of long-term efficacy studies

Category	Definition of the animal category	Start	Minimum duration
Salmon and trout	Growing salmonids	Trout ≥ 10 g Salmon ≥ 50 g **Comments:** • should efficacy studies start as soon as the fish have reach that weight or could the study start later? for example post-smoltification ? • smoltification leads to decreased feed intake and larger variability among animals and this may introduce problems of very high variability in the study	84 days
Rabbits	~~Rabbits that are reared for reproduction or meat production~~ All categories	1 week after birth **Proposal**: • setting as starting date 3 weeks after birth or after weaning • this considers that that rabbits only start eating solid feed from the age of +/- 18 days	42 days
~~Breeding does~~	~~Does that have become pregnant at least once~~	~~Insemination/mating~~	~~For effects on reproduction: Two cycles~~ ~~For effects on kits: preferably from 2 weeks before parturition until end of weaning period.~~
Horses	All categories		56 days

General requirements for the *in vivo* studies

Health status of animals

What means animals in “good health”?

- In recent opinions, some efficacy studies were disregarded by EFSA-FEEDAP based on the experts' assessment of the animal's health status
- Applicants have not received detailed information during post-opinion meetings following non-conclusive opinions
- Applicants would appreciate to receive indication on the expected thresholds for the main species
- It would avoid repetition of studies: increased costs and time for authorization. Not in line with 3R principles

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Health status of animals

We suggest:

- Including in the guidance an acceptable range of mortality and morbidity parameters for all species, in line with the current standards in EU farms
- Acceptance of studies in terms of animal health status subject to independent veterinary control at the start and during efficacy studies
- We consider that when health status at start is good, the study should be accepted.
- Only in exceptional cases (e.g., too high mortality not allowing for proper statistical analysis) a study should be subsequently discarded

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Health status of animals

- Possibility of using protocols that introduce stress factors, representative of “real life” conditions when carefully monitored by a veterinarian and approved by an ethical committee
- Especially relevant for "physiological condition stabilisers", intended to favourably affect the physiological condition of animals, including their resilience to stress factors
- The feed legislation through Commission Regulation (EU) 2020/354 acknowledges that feed additives, feed materials or compound feed can provide support to the animals in case of physiological disorders
- It should be possible to perform efficacy studies for PCS with stressors that generate physiological disorders (heat stress, weaning stress…)

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EU husbandry conditions

EFSA requirements aligned with Directive 2010/63/EU → may differ from the size requirements for housing units specified in Directives for commercial farms

Similar housing conditions to those of commercial farms should be permitted if the standards outlined in specific Directives are followed

- 98/85/EC, 2008/119/EC for calves, 2008/120/EC for pigs, 1999/74/EC for laying hens, and 2007/43/EC for chickens intended for meat production)

Deviations from official husbandry requirements should be allowed if:

- justified by the research model, subject to approval by an Ethical Committee (such as a veterinary authority in the local jurisdiction or university)
- done under the supervision of a licensed veterinarian

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Study type

- Field trials conducted under the supervision of a CRO, research institute, or licensed veterinarian should be allowed for all categories of feed additives to ensure their effectiveness in real-world conditions
- In certain situations, justified by the applicant, the limited availability of small pens on commercial farms may need accepting a lower threshold for statistical significance

  For example, a P-value below 0.1 instead of the standard 0.05, as currently applied for ruminants and pets

  This adjustment can be supported by the larger number of animals per treatment and the closer resemblance to the conditions in which the target species are kept

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THANK YOU!