UPDATED GUIDANCE ON THE ASSESSMENT OF THE EFFICACY OF FEED ADDITIVES – WHAT'S NEW

Jordi ORTUÑO (FEEDCO)
Alberto NAVARRO (FEEDCO)
Óscar GONZALEZ (FDP)

EUROPEAN FOOD SAFETY AUTHORITY

CHRONOLOGY

From 1 December 2024:

- Dossiers received **AFTER**: new Guidance document applies
- Dossier received **BEFORE**: some flexibility (new GD applies if new aspects favour the applicant)

Update of the EFSA FEEDAP Panel Guidance

TABLE OF CONTENTS

SCOPE OF THE GUIDANCE

Guide applicants in preparing the dossiers in assessing the efficacy of additives intended to be used in animal feed to demonstrate compliance with the requirements of Article 5.3 of Regulation (EC) No 1831/2003

Most common situations

Explain the rationale

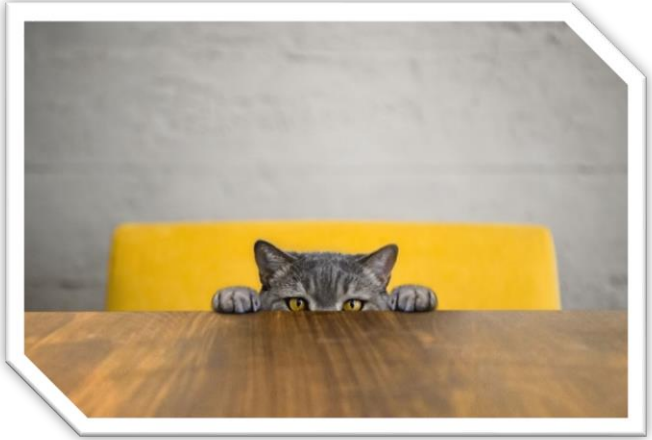
General principles of the efficacy assessment

GENERAL PRINCIPLES

First step: To establish the category and functional group (Article 6 + Annex I of Regulation 1831/2003)

- Studies based on the additive under assessment
- Lowest recommended use level *vs* appropriate control group
- **Independent studies** showing statistically significant effects on key endpoints related to the expected effect of the additive
- According to farming practices and animal welfare rules in the EU
- Following externally-audited quality assurance schemes
- Adequately reported and documented (standardisation)
- Attention to potential biological or physicochemical interactions

FOCUS ON THE EFFECT



Requirements for the different categories of additives

CATEGORIES OF ADDITIVES
(FUNCTIONAL GROUPS)

Technological additives

Effect on feed

- Preservatives
- Antioxidants
- Emulsifiers
- Stabilisers
- Thickeners
- Gelling agents
- Binders
- Anti-caking agents
- Acidity regulators
- Silage
- Denaturants
- Hygiene condition enhancers
- Other technologicals

Effect on animal

- Substances for the reduction of contamination of feed by mycotoxins
- Substances for control of radionuclides
- Other technologicals

Sensory additives

Colourants

- Substances that add or restore colour in feeds
- Substances which, when fed to animals, add colour to food of animals
- Substances which favorable affect the colour of ornamental fish and birds

Flavouring compounds

Coccidiotats and histomonats

Nutritional additives

- Vitamins, pro-vitamins and chemically well-defined substances with similar effect
- Compounds of trace elements
- Amno acids, their salts and aanalogues
- Urea and its derivatives

Zootechnical additives

- Digestibility enhancers
- Gut flora stabilisers
- Substances which favorably affect the environment
- Physiological condition stabiliser
- Other zootechnical additives

TECHNOLOGICAL ADDITIVES – EFFECT ON FEED

GENERAL RULE

- Type of study: *in vitro*
- How many: min. 3
- In which feed: representative range of feeds according to the intended use

No need for efficacy demonstration if…

…the product is already authorised for use in food **AND** similar effect is expected

Important: similar matrix!

TABLE 1 Endpoints for the demonstration of the efficacy of technological additives exerting their effect in feed.

Functional group	Endpoints for the demonstration of efficacy
Preservatives	Inhibition of the growth of spoilage microorganisms. The duration of the study should cover the period for which an effect is claimed. Test materials could be naturally or artificially contaminated.
Antioxidants	Protection against oxidative damage of key nutrients/components during feed processing and/or storage. The period for which a protective effect is claimed should be demonstrated.
Emulsifiers	Formation/maintenance of stable emulsions of otherwise immiscible or poorly miscible feeds.
Stabilisers	Maintenance of the physico-chemical state of feeds, including the use of coating agents.
Thickeners	Viscosity of the feeds.
Gelling agents	Formation of a gel resulting in a change in the texture of the feeds.
Binders	Pellet durability (hardness, abrasion) or energy consumed during pellet formation.
Anti-caking agents	Flowability (angle of repose, frictional forces, compressibility).
Acidity regulators	pH and/or buffering capacity in feeds.
Silage additives	Improved production/quality of silage (better preservation of nutrients). Inhibition of undesirable microorganisms. Reduction of effluents. Improved aerobic stability.
Denaturants	Indelible identification of feeds.
Hygiene condition enhancers	Reduction of contamination with specific microorganism(s) relevant to feed safety (e.g. potential human or animal enteropathogens or undesirable bacteria).
Other technological additives	The endpoints used to assess the function/effect of the additive should be defined and justified.

TECHNOLOGICAL ADDITIVES – EFFECT ON FEED

SILAGE ADDITIVES

- Substrate – well defined (DM, WSC, botanical origin)
- All fresh materials: easy, moderately-difficult, difficult to ensile (R429:2008)
- Four claims:
  - improvement of silage production/preservation of nutrients
  - aerobic stability;
  - reduction of effluents;
  - reduction of specific microorganisms (e.g., clostridia, Listeria spp).

HYGIENE CONDITION ENHANCERS AND/OR PRESERVATIVES

- Regarding # of feeds: general rule applies (3)
- All feeds (10 – 80%DM)
- # strains → depend on the claim (justification provided)
- Study should reflect actual CoU – min. 3 sampling points (start-intermediate-final)

TECHNOLOGICAL ADDITIVES – EFFECT ON FEED

Substances for control of radionuclide contamination

- Two groups fed with “contaminated” feed: control (unsupplemented) vs supplemented

Substances for the reduction of contamination of feed by mycotoxins

- Two groups fed with “contaminated” feed: control (unsupplemented) vs supplemented
- Studies using the animal category for which the lowest maximum content of the respective mycotoxin in feed is set
- Target mycotoxin content < legal/recommended levels

GENERAL RULE

- Type of study: *in vivo*
- How many: 3 (mycotoxins) / 1 (radionuclide) per species/category
- Duration: short-term (i.e., as much as needed to demonstrate the effect)

Potential extrapolation

- Two species covered (terrestrial): 3 covering growing + reproductive
- All terrestrial species: 1 in poultry, 1 in pig, 1 in ruminant (major species)
- + all aquatic: 1 in salmonids

SENSORY ADDITIVES - COLOURANTS

Studies needed!

No need for efficacy demonstration if…

…the product is already authorised for use in food **AND** similar effect is expected at similar level

- Type of study: *in vitro*
- How many: min. 3
- In which type of feed: representative range of feeds according to the intended use

- Type of study: *in vivo*
- How many: min. 3 per species/category
- Possibilities:
  - Reference to literature
  - Extrapolation from poultry/salmonids

SENSORY ADDITIVES - FLAVOURING COMPOUNDS

AIM:

DEMONSTRATION OF FLAVOURING PROPERTIES

Reference to literature

In vitro studies
(sensory panel / electronic nose)

Palatability claim:
3 *in vivo* trials
(per species/category)

NUTRITIONAL ADDITIVES

No need for efficacy demonstration for products authorised under Reg. (EC) 1831/2003

- Amino acids and their salts*
- Urea
- Vitamins and pro-vitamins
- Compounds of trace elements

Alternatively: 1 *in vivo* study

Substances ≈ vitamins:

Long-/Short-term based on nature + intended effect

Amino acid analogues / urea derivatives / new compounds of trace elements:

Bioequivalence or Bioavailability

Others:

Long-term study

ZOOTECHNICAL ADDITIVES

GENERAL RULE

- Type of study: *in vivo*
- How many: min. 3 per species/category

FOCUS ON THE EFFECT

Animal production or performance

- Long-term trials
- Exception: Enzymes – ***in vitro* trials allowed!**

Characteristics of animal-derived food

- Long- or short-term trials
- Justification of endpoints

Other effects

- Long- or short-term trials
- Justification of endpoints

ZOOTECHNICAL ADDITIVES

ENVIRONMENTAL IMPACT

- Reducing the output of N, P or trace elements – short-term (balance)
- Reducing the production of methane and other GHG – long-term (persistence of the effect)
- Reduce odours – min. 1 long-term
- Other effects – long/short + endpoints to be justified

ANIMAL WELFARE

- Long- or short-term + endpoints: justified based on substance and intended effect
- **Stress resilience**: challenges accepted
  - Stressing factors – Realistic situations
  - Challenge optimum physiological status and/or welfare
  - Clear link Stressor – Effect – Endpoint(s)
  - Endpoints: physiological ± behavioural ± immunological

COCCIDIOSTATS & HISTOMONATS

FLOOR PEN/BATTERY CAGE

- 5 years before submission
- Long-term

ANTICOCCIDIAL SENSITIVITY TESTS (AST)

- 2 years before submission
- Short-term

- How many studies: 3 of each
- Three groups: UUC / IUC / IT
- Endpoints:
  - Lesion/faecal score + OPT + morbidity + coccidiosis-related mortality
  - Zootechnical performance
- INOCULA:
  - Different regions from EU = unrelated Eimeria strains
  - Molecular characterisation
  - Virulence tests for each inoculum

Number of *in vivo* studies in food producing animals

Single animal category

- General rule: 3 studies per species and category
- Exemptions: nutritional / substances to control radionuclide contamination/ coccidiostats

Multiple categories of the same species

-food producing animals-

A. **Extension** – similar physiological/production stage: chickens for fattening → reared for laying/breeding

B. **No extension** – other categories at different production stage: chickens for fattening → laying hens

- Unless…claimed effect is the same between categories → 3 in one category +1 study in the other

Multiple species

-food producing animals-

- Unfeasible to perform studies in all potential target species: extrapolation is possible

A. **Physiologically similar species** → Table 4

- Animals kept for same purpose / Same intended effect

B. **Multiple species/categories** → Table 5

- Same intended effect
- Rationale: higher # species/categories → lower # studies

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

From	To physiologically related species
Chickens for fattening	Other poultry for fattening or reared for reproduction (e.g. turkeys, ducks, geese, pheasants, quail, guinea fowl)
Laying hens	Other birds kept for egg production or breeding[a] (e.g. turkeys, ducks, geese, pheasants, quail, guinea fowl)
Piglets[b] or pigs for fattening	Other porcine species for fattening and reared for reproduction
Sows	Other reproductive porcine species
Calves or cattle for fattening	Other bovines, ovines, caprines, cervids and camelids at the corresponding developmental stage
Dairy cows	Other dairy bovines, ovines, caprines, cervids and camelids
Horses	Other equines
Rabbits	Other leporids

[a]Limited to the effects demonstrated in the laying hens.

[b]Piglets: either weaned piglets or suckling and weaned piglets.

TABLE 5 Minimum number of independent studies and target species required for the assessment of efficacy in applications covering multiple species/categories of food-producing animals.

Application for	Number of studies required and species
All poultry for fattening and reared for reproduction	3 in chickens for fattening **or** 2 in chickens for fattening + 1 in turkeys for fattening
All poultry	2 in chickens for fattening + 2 in laying hens
All porcine species for fattening and reared for reproduction	3 covering both weaned piglets and pigs for fattening[a]
All porcine species	1 in weaned piglets + 1 in pigs for fattening + 2 in sows
All bovines, ovines, caprines, cervids and camelids for fattening and reared for reproduction	3 covering both calves and cattle for fattening[a] **or** 1 in calves + 1 in cattle for fattening + 1 in lambs or kids
All dairy bovines, ovines, caprines, cervids and camelids	3 in dairy cows **or** 2 in dairy cows + 1 in dairy sheep or dairy goat
All bovines, ovines, caprines, cervids and camelids	1 in calves + 1 in cattle for fattening + 2 in dairy cows
All rabbits	3 covering both growing and reproductive animals[a]
All insects	2 in honeybees + 2 in other insect species (one in each)
All insects except honeybees	3 in different species (one in each)
All terrestrial species	3 covering both chickens for fattening and laying hens + 3 covering both weaned piglets or pigs for fattening and sows + 3 covering both calves or cattle for fattening and dairy cows (if insects are included) + 3 covering both honeybees and other insect species
All fin fish	2 in salmonids (salmon or trout) + 2 in other fin fish species (one in each)
All crustaceans	3 in shrimp or other crustaceans
All aquatic species	1 in salmonids + 2 in other fin fish species (one in each) + 1 in crustacean or mollusc

[a]At least one study in each category should be performed.

REDUCED NUMBER OF STUDIES + INCREASED FLEXIBILITY

All poultry species

BEFORE		NOW	
All poultry species (chickens/hens, turkeys and minor growing and reproductive)	3 in chickens for fattening 3 in laying hens	All poultry	2 in chickens for fattening + 2 in laying hens

All "growing ruminants"

All growing ruminants (calves, cattle for fattening, sheep and goats for fattening, other minor growing ruminants)	3 in calves 3 in cattle for fattening	All bovines, ovines, caprines, cervids and camelids for fattening and reared for reproduction	3 covering both calves and cattle for fattening[a] **or** 1 in calves + 1 in cattle for fattening + 1 in lambs or kids

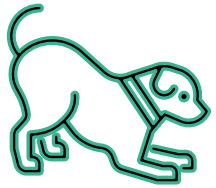
All terrestrial species

All poultry species (chickens/hens, turkeys and minor growing and reproductive)	3 in chickens for fattening 3 in laying hens	All terrestrial species	3 covering both chickens for fattening and laying hens + 3 covering both weaned piglets or pigs for fattening and sows + 3 covering both calves or cattle for fattening and dairy cows (if insects are included) + 3 covering both honeybees and other insect species
All pigs (piglets, pigs for fattening, sows and minor growing and reproductive porcine species)	3 in weaned piglets 3 in sows		
All ruminants (calves, cattle for fattening, cows, sheep and goats for fattening and dairy production, other minor ruminants growing and reproductive)	3 in calves 3 in cows		

PETS & NON-FOOD-PRODUCING ANIMALS

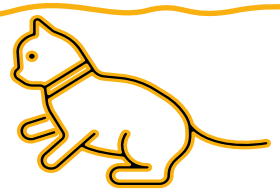
Efficacy demonstrated in food producing animals AND same intended effect

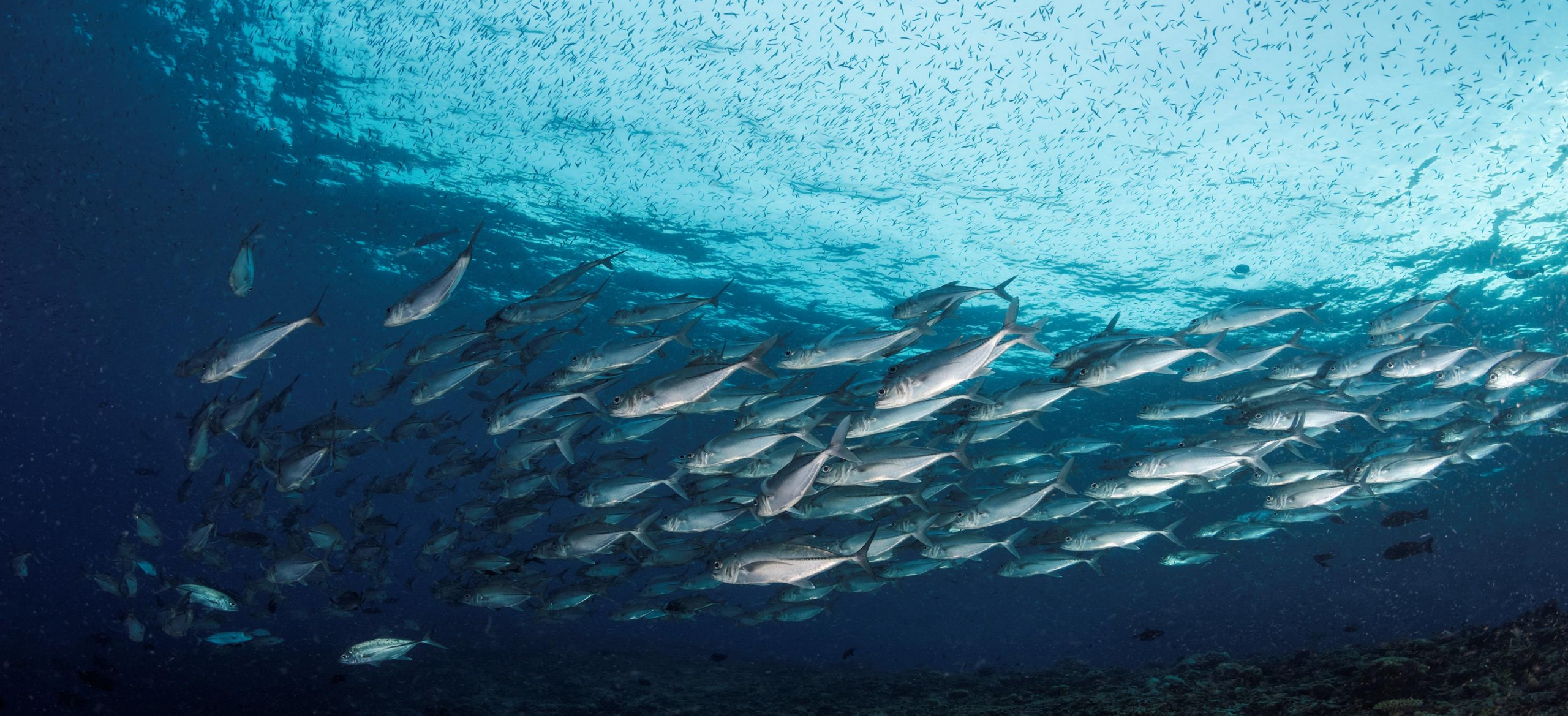
- 1 study needed /pet animal
- Maximum 3 species (for all pets)
- For ornamental birds - no studies needed if efficacious in chickens for fattening/laying hens
- For ornamental fish – no studies needed if efficacious in salmonids/fin fish



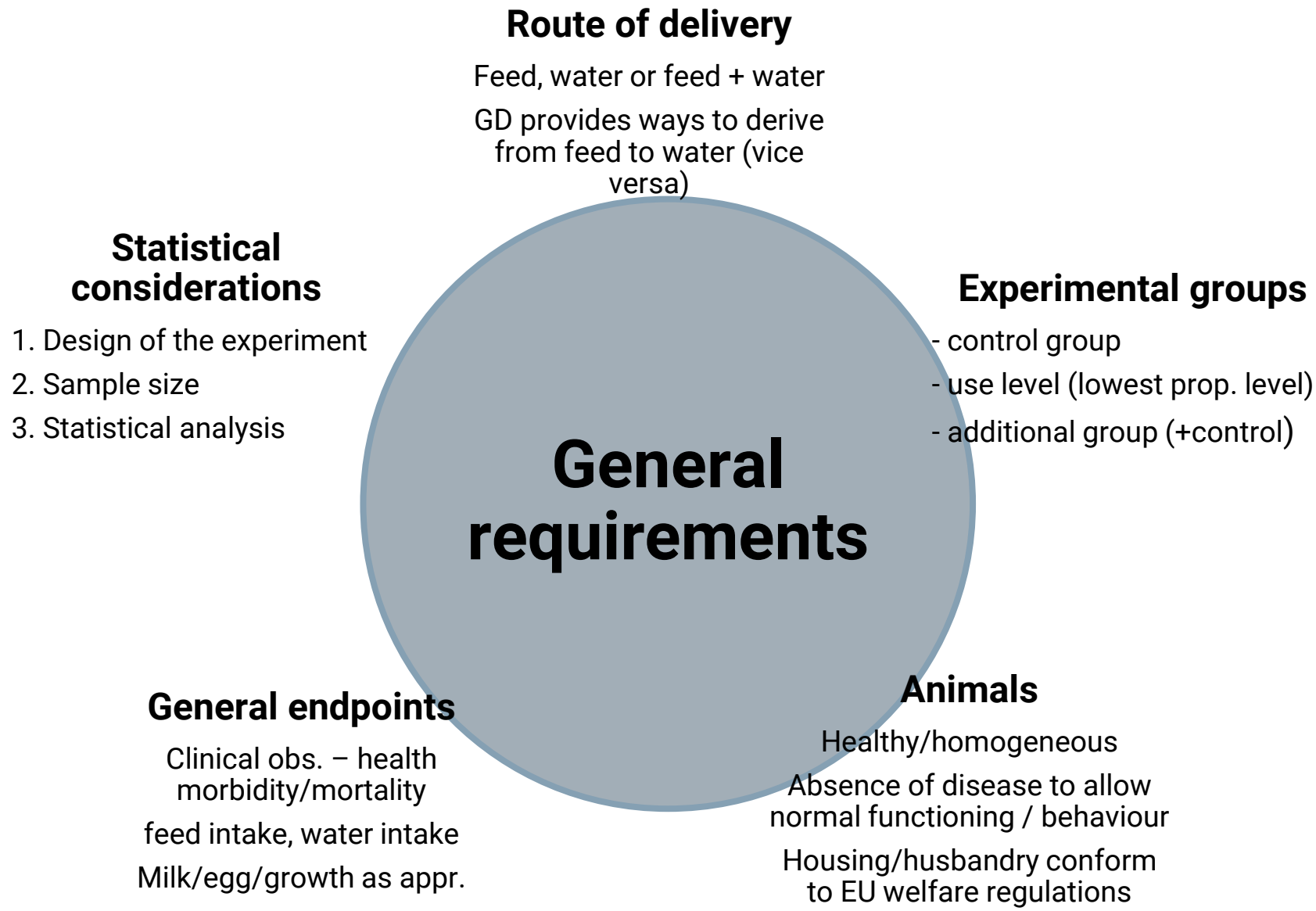
Efficacy not demonstrated in food prod. animals / Different effect

- General rule applies: 3 studies per species
- Two animal spp (e.g. cats & dogs): 4 studies covering both
- All pets – 4 studies covering cats & dogs + 1 additional in another spp.





General requirements on *in vivo* studies


Route of delivery
Feed, water or feed + water
GD provides ways to derive from feed to water (vice versa)
Statistical considerations
1. Design of the experiment
2. Sample size
3. Statistical analysis
Experimental groups
- control group
- use level (lowest prop. level)
- additional group (+control)
General requirements
General endpoints
Clinical obs. – health morbidity/mortality
feed intake, water intake
Milk/egg/growth as appr.
Animals
Healthy/homogeneous
Absence of disease to allow normal functioning / behaviour
Housing/husbandry conform to EU welfare regulations

MAIN NOVELTIES

Animal health

Design of the experiment should consider the variability in the response

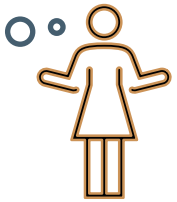
Ethical committee certificate

Directives 63/2010 EC and 698/58 EC

Orthogonal contrasts to compare use level *vs* control

LONG-TERM STUDIES

When should I perform LONG-TERM studies?



- Endpoints should be justified based on intended effect
- Non-exhaustive list provided in the GD:
  - Performance
  - Product quality
  - Environmental effects
  - Fecal consistency
  - Welfare: physiological, immunological, behavioral

For other species not included in the table:

- Growing animals – 42 d
- Adult animals – 56d
- Minor species – to follow similar periods as major species
- CoU shorter than these periods – Observation period ≥ 28d

TABLE 6 Minimum duration of long-term efficacy studies.

Category	Start of the study	Minimum duration
Chickens for fattening	1 day of age	35 days
Laying hens	< 30 weeks of age and ≥ 90% laying rate	84 days
Turkeys for fattening	1 day of age	84 days
Piglets (weaned)	≤ 7 days after weaning	42 days 35 days if the growth rate is ≥ 0.5 kg/day
Pigs for fattening	≤ 35 kg	Until slaughter, but not less than 70 days
Sows	For effects on reproduction: from insemination/mating For effects on lactation or on piglets: not later than from parturition	For effects on reproduction: two full reproduction cycles For effects on lactation or on piglets: until the end of the weaning period (but not less than 28 days)
Calves	< 6 weeks of age	56 days
Cattle for fattening	Full development of rumination and ≤ 12 months of age	84 days
Dairy cows	< 16 weeks after parturition and Milk yield ≥ 30 kg/day	84 days
Lambs/kids	< 8 weeks of age	56 days
Dairy ewes/goats	< 8 weeks after parturition	84 days
Rabbits (growing)	< 6 weeks of age	42 days
Breeding does	For effects on reproduction: from insemination/mating For effects on kits: no later than from parturition	For effects on reproduction: Two cycles For effects on kits: until the end of the weaning period
Salmon and trout	Trout ≥ 10 g Salmon ≥ 50 g	84 days
Honeybees		28 days
Other insects		Whole production cycle
Cats, dogs and other non-food-producing animals		28 days

SHORT-TERM IN VIVO STUDIES

What is considered a SHORT-TERM study?

Bioavailability/bioequivalence studies

- Bioavailability – absorption/transport of active substance to the tissue where it exert its function
- Bioequivalence – in vivo equivalence of two additives

Digestion/balance studies

- Discouraged with cannulated animals and in fish
- Adequate period of adaptation (min. 14d in ruminants and 7d other species)
- 5 days of excreta collection (all animals)
- Laying hens/dairy cows/sows to include measurement of the product output (milk/eggs, litter etc)
- For sows – use of gestating and lactating sows

Palatability studies

In vitro studies

IN VITRO EFFICACY STUDIES

- Aimed for additives affecting the characteristics of feed.
- Efficacy studies to be performed in laboratory-based studies

Requirements/recommendations:

- Providing certificate of analysis of the test item
- The study should cover a representative range of feeds (feed materials and/or complementary feed) to which the additive (water if appropriate)
- Confidence level of 95% to be used – Control vs treated group should be considered only
- Preferably parametric test (non-parametric also valid if number of observations is low)
- ≥4 replicates is recommended

Reporting of efficacy studies

REPORTING OF EFFICACY STUDIES

Applicants are invited to follow the recommendation stated in the GD (section 7)

Index

Title

Summary

Objectives

Materials and Methods:

- Ethical statement
- Animals housing and husbandry
- Study design
- Experimental procedures
- Statistical methods

Results

Discussion

Conclusions

Raw data/certificates of analysis

It is recommended that:

- The reporting should start with a trial protocol data sheet
- The reporting studies submitted that share a similar design should also be reported following a similar structure
- Applicants are encouraged to submit the raw data of the studies in a way that can be reviewed/edited (e.g. excel file)

EFSA Support for Applicants – How to forward questions on updated guidance documents

Info session – Updated FEEDAP Panel guidance document on Efficacy

Oscar Gonzalez, FDP Unit

4 December 2024

EUROPEAN FOOD SAFETY AUTHORITY

EFSA CATALOGUE OF SUPPORT INITIATIVES

Pre-submission phase

- **General pre-submission advice**
- **Ask a question***
- **SME** services
- **Renewal** PSA

Submission phase & Validity check

- **Clarification teleconference** after request for information

Risk assessment phase

- **Clarification teleconference** after additional data request

Post-adoption phase

- **Post-adoption** tele-conference

Info session and webinars on applications

Ad-hoc meeting with food and feed business representatives

Scientific workshops and conferences

Ask a Question *

Follow-up teleconference on web form query

Fast processing of web form queries by SMEs

* Ask a question is available at any point of the lifecycle of an application. In the context of this Info-session, it is presented in the pre-submission phase

QUESTIONS DURING THE PREPARATION OF THE APPLICATION

Two services available, so the applicant can address doubts to EFSA,
even in very early stages of the preparation of an application

efsa CONNECT

on the rules and content
of an application:

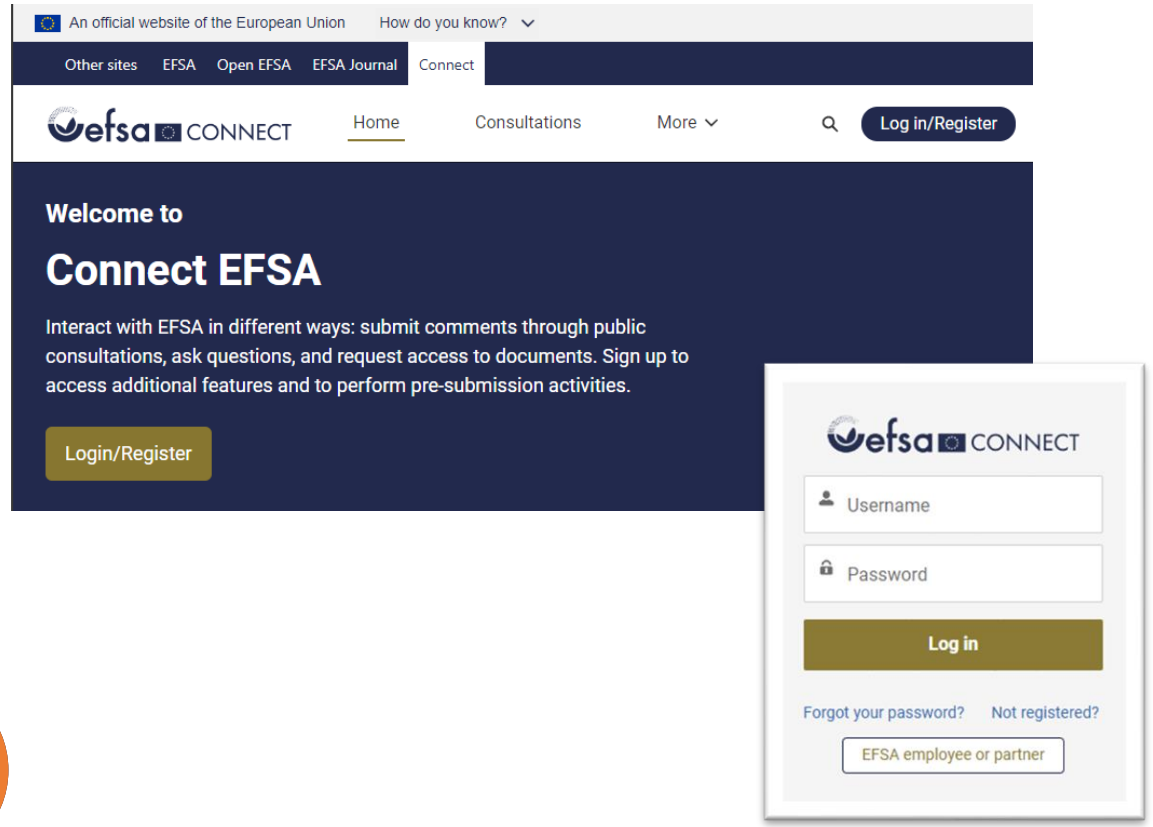
General pre-submission advice

other questions
(procedural steps, IT tools…):

Ask a Question

HOW TO ADDRESS THOSE QUESTIONS TO EFSA?

Log in the **Connect.EFSA** platform → and then:



- **Follow three simple steps** to request EFSA's **General pre-submission advice** or
- **Send a query** via the **Ask a Question** service

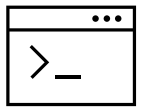
SME-TAILORED SERVICES

Fast processing of **Ask a Question** queries

- reply within 7 working days instead of 15

Fast-tracking of **General pre-submission advice** requests

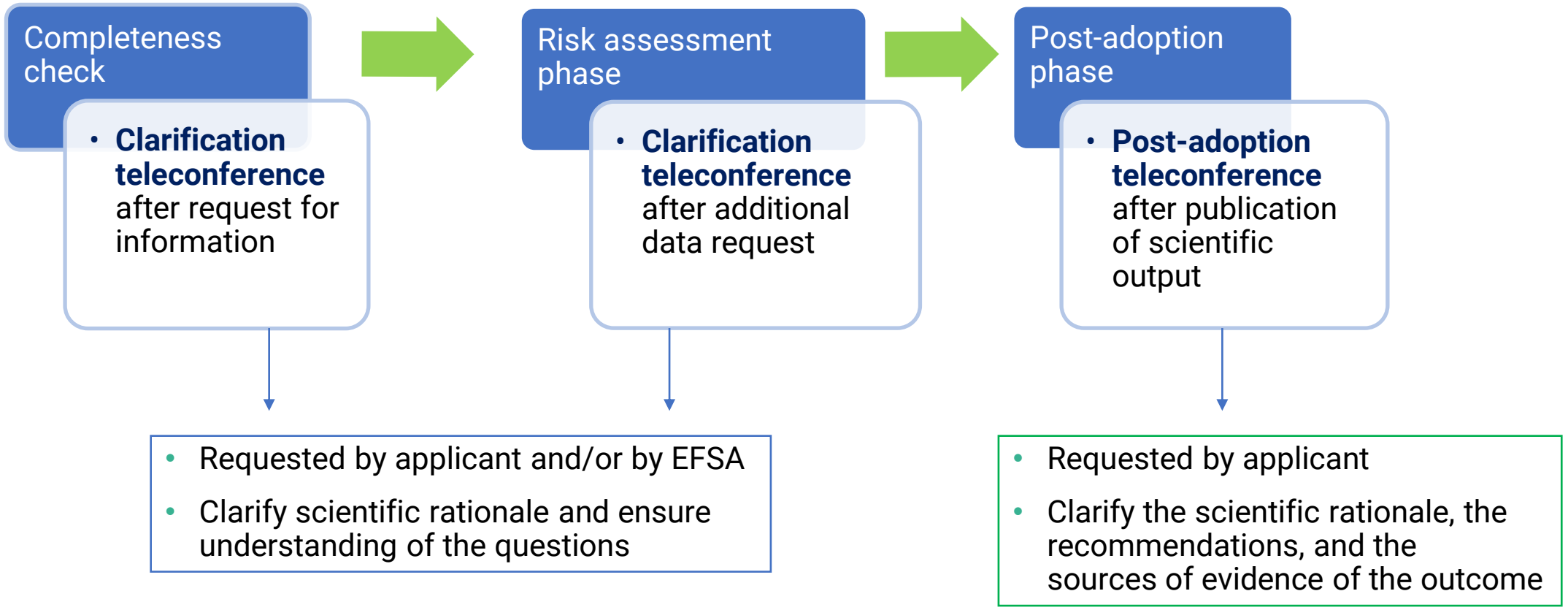
- reply in a **tele-meeting** and in 50% of the standard timeline



Dedicated support on the **use of IT tools** for preparing an application

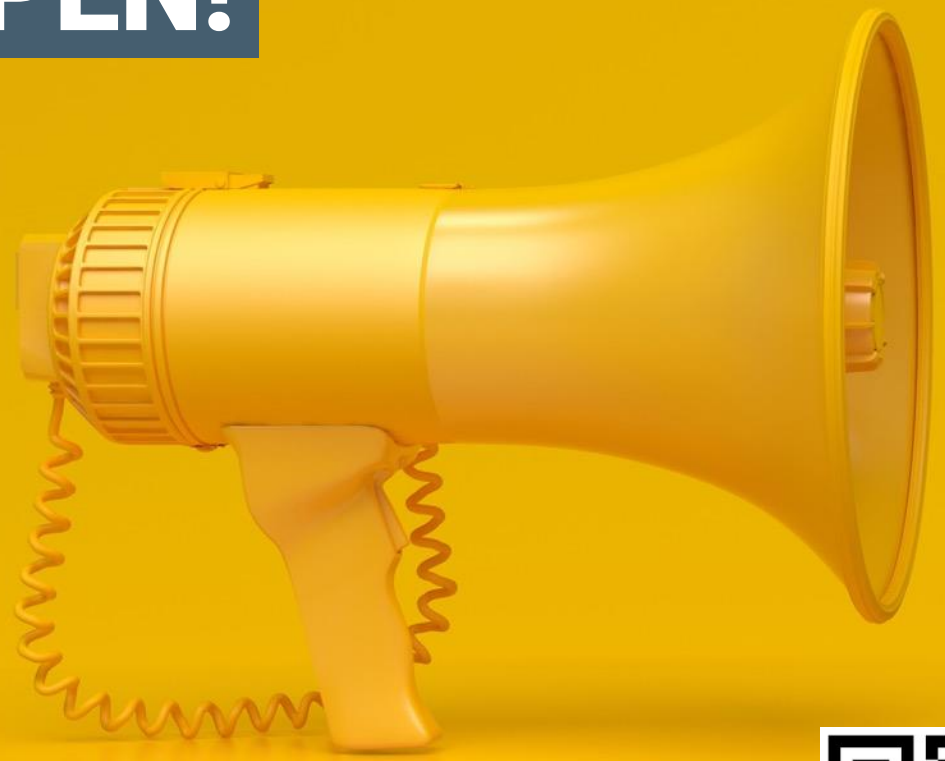
- physical or virtual hands-on session in the use of IT tools (Connect.EFSA, ESFC…)

SERVICES AFTER THE SUBMISSION OF THE APPLICATION



Which service fits my needs? send a query to **Ask a Question**

CALL FOR INTEREST OPEN!



Join EFSA's new stakeholder community on applications for food and feed products!

Express your interest by
10 January 2025