# GUIDELINES FOR PRESENTING A TECHNICAL REPORT ON ZOOTECHNICAL AND TECHNOLOGICAL ADDITIVES (MICOTOXIN ADSORBENTS AND SILAGE INOCULANTS

## Introduction

The legislation for registration and use of these products is regulated in the regulation approved by Decree 6,296, of December 11, 2007, Normative Instruction 13 of November 30, 2004 and Normative Instruction 15, of May 26, 2009.

Zootechnical additives, according to their functions and properties, shall be classified into functional categories and groups, as provided for in IN 13/2004.

## Zootechnical additives

Zootechnical additive: any substance used to positively influence the improvement of the performance of animals.

a) Digestive: substance that facilitates the digestion of ingested food, acting on certain raw materials intended for the manufacture of products for animal feed: Digestive:

a.1 Digestive additives: enzymes that are proteins that are proteins that are bound or not to cofactors, which have specific catalytic properties.

b) Flora balancers: microorganisms that form colonies or other chemically defined substances, which have a positive effect on the flora of the digestive tract:

b.1 Probiotics: are strains of living (viable) microorganisms, which act as auxiliaries in the recomposition of the microbiota of the digestive tract of the animals, contributing to their balance;

b.2 Prebiotics: ingredients that are not digested by the digestive enzymes of the host, but that are fermented by the microbiota of the host digestive tract of animals, contributing to their balance;

b.3 Acidifiers: organic or inorganic acids that reduce the pH of the upper digestive tract, with the aim of facilitating digestion and contributing to the balance of the microbiota of the digestive tract.

c) Performance enhancers: chemically defined substances that improve productivity parameters, excluding antimicrobials and anticoccidians, which have become registered as veterinary products.

d) Other zootechnical additives.

This roadmap also applies to technological additives classified in the functional groups called mycotoxin adsorbents and silage inoculants (Normative Instruction 51, of August 3, 2020) and partially, as described below, for the authorizations of new raw materials for use in additives, as disciplined in Normative Instruction No. 40, of June 15, 2020.

## 1. Technical report

The applicant must submit his/her request for registration, change or renewal through SipeAgro. **When it comes to registration of raw material for the manufacture of an additive, the user must inform this situation in the "attach file" tab of the system.**

The information referring to items 1.1 to 1.6 of the technical report must be inserted directly in the corresponding fields of SipeAgro and the others attached, in order to compose the technical-scientific dossier. For the registration of additives, items 2.1 to 2.12 apply, except for item 2.9.1, observing the considerations described in each topic. **While for the registration of raw materials used in the manufacture of additives**, items 2.1 to 2.8, 2.9.2 and 2.12 apply, considering the particularities mentioned in each item.

Requests for **authorizations of new raw materials** must be made through the Electronic Information System-SEI, following the script of Normative Instruction No. 40, of June 15, 2020, and safety and efficacy studies must follow the rules present in items 2.9.1, 2.9.2 and 2.11.

For changes, the holder of the product registration must identify them. Those that do not modify the identity characteristics initially approved of the product, that is, the changes regarding the name, size of the packages and quantitative and / or qualitative of the vehicle, provided that it is of the same chemical and physical nature, it is necessary to present only technical justifications by the Technical Responsible for such

changes. However, changes related to composition, mode of use, dosages, animal species or categories and shelf life, will have the same requirements for the new registration, and may present technical justification for the absence of any document or information. Upon renewal, the information and documents mentioned in item 2.13 must be updated.

The applicant shall present the main characteristics of the additive and structured as follows:

1.1 Product name and trademark;

1.2 Classification of the additive;

1.3 Qualitative and quantitative composition (active substance/agent, other constituents and impurities);

1.4 Physical form of product presentation, characteristic of packaging and form of packaging;

1.5 Indications for use and animal species;

1.6 How to use;

1.7 Inscription of the substance and crude and structural formula, molecular weight;

1.8 Summary of the manufacturing process;

1.9 Report of safety studies;

1.10 Report of stability studies;

1.11 Report of efficacy studies;

1.12 Certificates and documents required for imported product;

1.13 Other relevant documents and other information;

1.14 List of documents considered confidential, considering the Access to Information Law (LAI) (Law No. 12,527, of November 18, 2011), if applicable.

## 2. Product data.

### 2.1 Product designation by name and trademark

The change of the original name of the imported product will only be allowed upon the prior authorization of the establishment abroad by means of a duly signed authorization document.

### 2.2 Classification of the additive according to the main effect

To start the registration of additive, it is necessary to propose the classification of the product by category, functional group and main effect, according to item 3.5 and annex II of Normative Instruction 13/2004, such as: Zootechnical additive (category) digestive (functional group) – enzymatic (main effect); zootechnical additive (category) Flora balancer (functional group) – probiotic (main effect); zootechnical additive (category), performance enhancing additive (functional group), beta agonist (main effect), etc. For products composed of active substances of a distinct category or functional group or main effect, they should be classified on the basis of the main effect of the product as proven by the efficacy test.

### 2.3 Inscription of the substance and crude and structural formula, molecular weight

Chemically well-defined substances shall be described by the generic name or chemical name according to the IUPAC (International Union of Pure and Applied Chemistry) nomenclature or other international generic names and abbreviations and/or CAS (Chemical Abstracts Service) Number.

The raw materials must comply with the standard of identity and purity, safety and specifications established by the Chemical Abstracts Service - CAS, Food Chemicals Codex - FCC, or other internationally recognized references, and must, therefore, prove their registration in said publications.

For enzymes, the number and systematic name proposed by the International Union of Biochemistry (UIB) in the most recent edition of the "Nomenclature of Enzymes" should be provided for each declared activity. For activities not yet included, a systematic designation consistent with the UIB nomenclature rules shall be used.

For bacteria, the names used must be in accordance with the International Code of Prokaryote Nomenclature, as established by the International Committee on Systematics of Prokaryotes. New taxonomic units or reassignments to taxonomy and nomenclature are published in the International Journal of Systematic and Evolutionary

Microbiology (IJSEM). The nomenclature and taxonomy of fungi are established by the International Code of Nomenclature for algae, fungi and plants. The currently approved nomenclature for fungi can be found in the MycoBank database.

For products containing chemically defined active substances in their formulation (e.g. acids, enzymes, etc.), the crude and structural formula and molecular weight according to the international nomenclature must be presented in the technical report (annex in SipeAgro).

2.4. Qualitative and quantitative composition

All the raw material that makes up the formulation of the product must be previously approved and published by MAPA.

For products made with more than one raw material, including active substances and auxiliaries (anti-binder, vehicle, antioxidant, etc.), it will be necessary to describe them separately with their respective proportion in SipeAgro, and must also define the function and technically justify the use of each raw material by the manufacturer in a document attached to the system. In these products, only the raw material(s) with function(s) related to the effectiveness of the product shall have its active substance(s) guaranteed, in the specific unit(s), according to the legislation. The guaranteed active substances shall be correlated with the starting material in the composition and shall be in line with the certificate of analysis of at least three batches of the product.

When using microorganisms in the manufacture of the product, either as an active substance or strain/strain producing some raw material, such as enzymes and cell wall, the taxonomic classification of each microorganism as published in the international codes of nomenclature (CNI) will be mandatory. The strains/strains shall be deposited in an internationally recognised culture collection and a certificate of deposit issued by the collection shall be provided, specifying the accession number under which the strain/strain is kept.

For products and their respective raw materials that contain or are produced from Genetically Modified Organisms (GMOs) it will be necessary to present documentation for evaluation and legal authorization, in accordance with Law 11.105 of March 24, 2005. It is also mandatory for the manufacturer to issue a declaration when the raw materials and products do not contain or are not derived from GMOs.

For enzymes, the guarantees shall be expressed in units of activity per gram (U/g) as a function of appropriate and chemically pure specific substrates. For

microorganisms, the guarantees should be expressed in number of colony-forming units per gram – CFU/g. The other active substances are guaranteed in mg/kg or g/kg, as defined in the legislation.

### 2.5. Manufacturing Process

It shall briefly describe the manufacturing process of the product by means of a flowchart and shall provide a description of the production process (e.g. chemical synthesis, fermentation, cultivation, extraction of organic material or distillation, filtration, purification, etc.) used in the preparation of the active substance of the additive, the composition of the fermentation/cultivation media and the purification methods.

It should also detail the information regarding the controls carried out on raw materials and finished products. In the control of raw materials it will be necessary to present the analyses performed and their frequencies. For finished products, it must inform the analyses carried out and their frequencies, and must contain, at least, chemical, physical and microbiological analyses of conformity and mainly of the active substance(s) contained in the guarantee and respective reports signed by the technician responsible for the analysis. The methods of analysis of the finished product should be described, if it is for internal use of the company, or only cited, when it is already published.

#### 2.5.1. Other substances and impurities.

Where there are substances with toxic or other undesirable properties or which are not intentionally added and which do not contribute to the activity of the additive or with impurities, these shall be identified and quantified in the dossier. In addition, for fermentation products, it must confirm the absence of producing organisms in the additive, describing the residues generated in the process and the controls carried out on them, such as: physical, chemical and microbiological analyses, quantification, method of separation and purification of the raw material, destination, etc.

When there are no toxic substances and/or impurities, the manufacturing company must present a document that technically justifies the purity and conformity of the raw materials and the finished product through the controls carried out in the manufacturing process and good manufacturing practices.

### 2.6. Physical form of the product, characteristic of the packaging and shape of packaging

All forms of presentation of the product should be described in a clear and objective manner to facilitate identification by the consumer and, whenever possible,

related to the packaging. The characteristics of the packaging must contain, at least, the shape, size, material used and liquid content, and be in accordance with the environmental temperatures recommended in the legislation that deals with the stability test (Normative Instruction 15, of 02/12/2005). The conditions and form of storage must be aligned with the stability test, and should inform the characteristics of the place, such as: humidity, light, temperature and other care, such as the use of pallets, distance from the walls, out of reach of children, etc. It should also contain the necessary care after opening the package, if applicable.

### 2.7. Indications for use and species/category of animal

In this item, it should describe only the positive effects of the additive on the performance of animals that have shown scientific evidence in the efficacy test of the product concerned, specifying the strengths, period, species and categories of animals that have obtained demonstrably satisfactory results in those tests for the target species. For products that present side effects to their main objective, obtained in the efficacy test or in a review of scientific literature, which relate or assist in the improvement of animal performance, provided that it is not of therapeutic or drug action, they may be highlighted in the indication for use. Possible contraindications of the product in this field should also be mentioned. If there are relevant physicochemical interactions, it is necessary to add information and evidence that attest to the incompatibility with other additives, drugs, nutrients, etc., that may compromise the safety and efficacy of the product, presented in items 2.9 and 2.11. For raw materials intended for the manufacture of additives, it may not contain an indication of species and animal category in the registration and label, and must contain the following sentence:

**"Raw material for exclusive use by xxxxx for the manufacture of xxxxxx additives. The commercialization or any other form of direct distribution to the rural producer and the direct use in feed, concentrates, supplements, cores, premixes and other products for animal feed are prohibited."**

### 2.8. How to use

In this item, you should describe the care and information on how to add the product to premixtures and / or directly to products intended for animal feed or water. It will also be necessary to define the quantities to be administered for each category and animal species and the period, which may contain the minimum and maximum dose of the product. In this field, it should be noted that any change in the administered amount

of that mentioned on the label will have to be under the guidance of the professional specialized in the area or responsible technician, provided that the dosage is within the safe limit for the species and category of target animals defined in the product safety studies and expressed on the label.

It should also be noted that this item should include all recommendations regarding the safety of use of the product for the target species and category of animals, the consumer and the environment in accordance with the safety studies presented (**tolerance study for each of the species and categories of target animals, in the case of products absorbed by animals)**.

Acrescenta-se neste tópico, as medidas essenciais de prevenção dos riscos e os meios de proteção na fabricação e na utilização, conforme descrito no item 2.9.2.

This topic adds the essential risk prevention measures and the means of protection in manufacturing and use, as described in item 2.9.2. For raw materials intended for the manufacture of additives, it may not contain in the registration and label any information on the quantity to be administered to the category and animal species, and the following sentence shall be included:

"**Use the raw material in accordance with the instructions of the company xxxxxx for the exclusive use in the manufacture of xxxxx additives**".

2.9. Safety studies

2.9.1. Safety with regard to target animals, the consumer and the environment

For authorization of raw material intended for the manufacture of the additives addressed in these guidelines, it will be necessary to present studies regarding the safety of the product or technically based justifications for the exemption of each study, and should address the following topics: safety of use of the additive in target animals; risks associated with the selection and/or transfer of antimicrobial resistance and increased persistence and spread of enteropathogens; risks to the consumer arising from feedingstuffs derived from animals containing or treated with the additive or from residues or metabolites thereof; risks of inhalation and contact with other mucosal tissue, eyes or skin for persons likely to handle the additive; and risks of harmful effects on the environment arising from the additive itself or from products derived from it, either directly or excreted by animals.

However, **for the registration of additives**, studies related to the safety of use in target animals, transfer of resistance and safety to the consumer are exempt from being included in the dossier; will be considered those presented when authorizing the

raw material. However, other product safety studies related to the handler/user and environment must be included at the time of registration of the additive. The proofs of such studies may be made through the presentation of the technical safety data sheet (MSDS – Chemical Safety Information Sheet), which must comply with Brazilian (ABNT) or international rules.

For companion animals it will not be necessary to present the studies on safety for the consumer and the environment. Regarding the registration of probiotic products, it is assumed that the intrinsic resistance of the microorganism presents a minimum potential for horizontal dissemination, while resistance mediated by genes found in mobile elements of the genome is considered to have a high potential for horizontal dissemination. Therefore, all microbial strains that are candidates for probiotics should be evaluated for susceptibility to a relevant number of antimicrobials of human and veterinary importance. In this context, to define the profile of resistance to antimicrobials should follow the guidelines contained in the guide for procedural instruction of petition for evaluation of probiotics for use in food of the National Health Surveillance Agency in the topic that deals with the profile of resistance to antimicrobials of clinical importance (Anvisa, Guide 21/2019 - version 1).

For silage additives, they shall be exempt from submitting studies on the safety of use of the additive in target animals, for consumers and for the environment where it can be demonstrated that: no detectable amount of the relevant active substance(s) or metabolites or the active agent(s) survive in the feed at the end or the active substance(s) and agent(s) occur as a normal silage component, and The use of the additive does not substantially increase its concentration compared to silage prepared without the use of the additive.

2.9.2. Risk prevention measures and means of protection in manufacture and use

Depending on the studies presented in item 2.9.1 on toxicological and exposure risk assessment in relation to the safety of handlers/users, such as: the effects on the respiratory system, eyes, skin, systemic toxicity and exposure assessment, preventive measures should be proposed to reduce or eliminate exposure, and in addition, may propose the use of personal protective equipment to prevent residual risks.

For chemical and biological products, based on safety studies, the technical safety data sheet must be provided in accordance with Brazilian (ABNT) or international rules.

2.10. Stability study

In order to define the provisional or definitive shelf life of the additive, the company shall submit the accelerated or long-term stability test of the active ingredient(s).

To grant a provisional shelf life of the additive with indication of storage in original packaging at room temperature, an accelerated stability test may be presented, conducted in an air-conditioned chamber at: 40ºC ± 2ºC/75% ± 5% RH, for a period of 6 (six) months or 50ºC ± 2ºC/90% ± 5% RH, for a period of 3 (three) months.

To grant the definitive shelf life of the additive with indication of storage in original packaging at room temperature, the test should be conducted at 30ºC ± 2ºC/65% ± 5% of Relative Air Humidity -RH (climatic zone 4), for the period of the proposed validity.

For products whose recommendation is to store under refrigeration, frozen or other storage conditions outside climatic zone 4, the procedure is similar to that described for products stored at room temperature, with the exception of critical temperatures.

At the time of registration, the company will have the option to submit only the completed accelerated stability test, in order to grant the provisional validity period, along with the respective schedule of execution of the long-term stability test. However, it will be necessary after completion of the long-term stability test, to present it in order to ratify or rectify the period of validity initially granted.

If the nature of the active substance of the additive does not allow the performance of the accelerated stability test, in the absence of the long-term test completed at the time of the application for registration of the additive, the company must submit the project of the long-term stability test referred to, being granted provisional validity of 06 months, until completion of the long-term test.

Companies pending submission of the results of the long-term stability test at the time of granting registration will be subject to specific supervision to this requirement and, on renewal of the product registration, will be re-evaluated on this requirement for its approval.

There will be no need to present the validation data of the analytical methods used to measure the active substance(s), but you must cite the method, when it is published or describe it, when it is for internal use of the company.

In order to reduce the number of batches of the product to be submitted to the stability test, companies will be able to demonstrate the similarity between batches

through appropriate physico-chemical tests. The similarity is the demonstration that three or more batches were manufactured according to the same production process and that the quality controls of the finished product meet the recommended specifications. After demonstrating the similarity, the company will be able to randomly choose one of the three lots to carry out the stability studies. For the similarity to be proven, it will be necessary to present an analytical report of each batch of at least: of the active substance(s) or marker(s), moisture, particle size and coloration. The values of the analyzed parameters obtained between and within the batches must be within the statistical limits validated by the company in the production process of the additive.

The stability test shall be submitted by means of the stability report, containing:

1 - Product Name;

2 - Number of batches or replicas of the additive;

3 - Storage conditions;

4 - Type of material used in primary packaging;

5 - Description of the stability study plan adopted.

6 - Reference or description of the analytical methods used;

7 - Statistical trend analysis for the accelerated stability test;

8 - Statistical analysis between batches in long-term stability;

9 - Test results, which can be presented with the help of tables, graphs and chromatograms;

In order to avoid the presentation of raw test data, the report should contain the mean values of relative humidity, temperature, of the active substances or markers accompanied by standard deviation, standard error of the mean and coefficient of variation.

Mycotoxin adsorbent additives composed only of raw materials of inorganic origin are exempt from the presentation of the stability test, but for the other mycotoxin adsorbent additives the same rules in this script apply.

For these adsorbents, it may also, in the stability test, replace the quantification of the active substance(s) or markers by measuring the adsorption capacity of the mycotoxins obtained in the in vitro tests, and should describe the quantification

technique. In order for the stability test to be considered compliant, the values obtained from the active substance(s) or markers must be within the statistical limits of product specification and the declared guarantee limits.

For enzymes, stability should be measured in terms of loss of catalytic activity and for microorganisms in terms of loss of viability. For chemicals or mixtures, stability should be assessed by monitoring the content of one or more guaranteed active substances.

To express on the label the stability of the additive in the different forms of thermal processing, such as pelletizing and extrusion, it will be necessary to perform the stability simulating these situations of use, in accordance with the rules established in this roadmap, where appropriate. If the company does not have these studies at the time of registration of the product, it may not make any mention on the label or advertising that induces third parties to use the product as if it were stable to thermal processing.

When the stability test is not presented for the registration of raw materials for the manufacture of additives, the validity field should contain the following sentence: "**The shelf life of the raw material should be consulted directly with its manufacturer**".

### 2.11. Efficacy study

The studies shall demonstrate the effectiveness of the additive (not the raw material(s) that make up the additive) on the animal performance and/or quality of products of animal origin. The hypotheses of the research must be proven according to the function of the additive and for species and animal category.

For all additives intended to have an effect on animals, in vivo studies will be required, while for categories of additives without a direct effect on animals, in vitro efficacy studies, such as some silage inoculants, should be submitted.

The experimental protocol should be carefully elaborated by the person responsible for the research, describing the methodology, material used, the species and animal categories, number and conditions under which they were housed and fed, and statistical analysis of the data. Studies should be conducted in such a way that animal health and rearing conditions do not adversely affect the interpretation of the results. Studies should demonstrate the efficacy of the additive at the lowest recommended dose, through sensitive parameters, in comparison with a negative and,

optionally, positive control group, in at least one study with protocols based on the scientific literature, which may be carried out in other countries. Such studies may also include the maximum recommended dose where the additive is proposed. In general, the duration of efficacy studies corresponds to the requested application period or minimum period for the respective target animal species and categories as recommended in Table 1.

Known or potential biological or chemical interactions between the additive, other additives and/or veterinary medicinal products and/or feed constituents where this is relevant to the efficacy of the additive concerned (e.g. compatibility of the microbial additive with coccidiostats or organic acid) shall also be considered in the efficacy studies.

The experimental design should take into account the appropriate statistical power and risks of types 1 and 2. The protocol must be sufficiently sensitive to detect any effects of the additive at the lowest recommended dose (type 1 α risk, $P \leq 0.05$ in general and $P \leq 0.1$ for ruminants, pet animals and non-food-producing animals) and have sufficient statistical power to ensure that the experimental protocol meets the objective of the study. The risk of type 2 β is less than or equal to 20% in general, and 25% for research on ruminants, companion animals and non-food animals, which gives rise to a power (1-β) greater than or equal to 80% (75% for ruminants, pet animals and non-food production animals).

Depending on the properties and purpose of the additive, the resulting measures may be based on performance characteristics (e.g. feed efficiency, average daily gain, increase in animal products), carcass composition, herd performance, breeding or animal welfare parameters.

Table 1 defines the species and categories of target animals for long-term efficacy studies as well as the minimum experimental duration. However, some studies on metabolism, such as digestibility, bioavailability, nutrient balance, among others, can be performed in shorter periods than those established in the referenced table, normally these studies should have an average duration of seven and fourteen days for monogastric and ruminant animals, respectively.

Table 1 - Minimum duration of long-term efficacy studies.

| PIGS | | |
|---|---|---|
| **Species/categories** | **Category description** | **Trial period (minimum)** |
| Infant piglets | Suckling piglets in the sow | 14 days |
| Weaned piglets | Pigs in the nursery phase | 42 days |
| Pigs growth/finishing | Pigs in the growth and finishing phase | 58 days |
| Breeding sows | Females fertilized/mated at least once | From covering to the end of the first weaning (a cycle) |
| Lactating sows (in order to benefit piglets) | Females fertilized/mated at least once | At least two weeks before calving until the end of the weaning period |
| **POULTRY** | | |
| **Species/categories** | **Category description** | **Trial period (minimum)** |
| Broiler chickens | Chicken in initial phase | 14 days |
| Broiler chickens - fattening | Chicken fattening | 35 days |
| Pullets for laying | Poultry reared for egg production or breeding purposes | 112 days (if efficacy data are not available for broilers) |
| Laying hens | Productive poultry kept for egg production purposes | 112 days |

| | | |
|---|---|---|
| Beef turkeys | Poultry reared for fattening | 84 days |
| Breeding turkeys (females and males for breeding) | Female and males bred for breeding | 6 months |
| **CATTLES/BUBALINOS** | | |
| **Species/categories** | **Category description** | **Trial period (minimum)** |
| Infant calves (milk or beef) | Calves reared for breeding or beef production | 56 days |
| Calves for calf production | Calves for calf production | 84 days |
| Cattle for fattening | Cattle for meat production | 84 days |
| Lactating cows | Females that have produced at least one calf | 84 days |
| Breeding cows | Females fertilized/mated at least once | From covering to the end of the first weaning (a cycle) |
| **OVINE** | | |
| **Species/categories** | **Category description** | **Trial period (minimum)** |
| Lambs for breeding | Lambs raised for breeding | 56 days |
| Lambs for fattening | Lambs raised for meat production | 56 days |

| | | |
|---|---|---|
| Lactating ewes | Ewes that have produced at least one lamb | 84 days |
| Breeding sheep | Females fertilised/mated at least once | From covering to the end first weaning (a cycle) |
| **GOATS** | | |
| **Species/categories** | **Category description** | **Trial period (minimum)** |
| Goats for breeding | Goats bred for breeding | 56 days |
| Goats for fattening | Goats raised for meat production | 56 days |
| Lactating goats | Goats that have produced at least one goat | 84 days |
| Goats for breeding | Females fertilized/mated at least once | From covering to the end of the first weaning (two cycles) |
| **FISH/SHRIMPLOTS** | | |
| **Species/categories** | **Category description** | **Trial period (minimum)** |
| Fattening | Raised for meat production | 90 days |
| Breeding | bred for breeding | 90 days |
| **RABBITS** | | |

| Species/categories | Category description | Trial period (minimum) |
|---|---|---|
| Infant and weaned rabbits | | 56 days |
| Rabbits for fattening | Rabbits reared for meat production | 42 days |
| Lactating rabbits (in order to benefit young rabbits) | Rabbits fertilized/mated at least once | From the cover to the end of the first weaning (a cycle) |
| Rabbits for reproduction | Rabbits fertilized at least once | Desde a cobertura até ao final primeira desmama (um ciclo) |
| **Species/categories** | **Category description** | **Trial period (minimum)** |
| **EQUIDAE** | - | 56 days |
| **PET ANIMALS OTHER THAN EQUIDAE** | - | 28 days |

*Source: adapted from REGULATION (EC) No 429/2008*

Additives for use in silage must demonstrate their effectiveness in at least one of the following relevant parameters, such as: improvement of silage production; inhibition of undesirable microorganisms; reduction of effluents and improvement of aerobic stability.

In the specific case of mycotoxin adsorbents, efficacy should be demonstrated by at least one short-term in vivo study (mean 7 and 14 days for monogastric and ruminant animals, respectively) per animal species. When the aim is to indicate to all terrestrial animal species and categories, efficacy should be demonstrated in three main species (at least one study in each), representing the different digestive systems (birds, non-ruminant mammals and ruminants). For additives intended for fish, specific studies with this species will be required. In general, the excretion of mycotoxins or metabolites in faeces or urine, concentration in blood or plasma or serum, tissues or products (milk or eggs) or other relevant biomarkers can be considered as relevant parameters to

demonstrate the effectiveness of the product, as well as zootechnical ones. **However, it should be noted that studies should demonstrate a positive effect on the parameter(s) directly correlated with the mycotoxin(s) tested for the respective target animal species and categories.**

Extrapolation of interspecies efficacy data can be applied only in the case where the animals are physiologically comparable, kept for the same purpose, i.e. reproduction or meat production (including milk or egg production) and the mode of action is considered the same between the species and the claimed effects as well. When such a link cannot be made, efficacy is demonstrated as set forth in this topic.

In order to pragmatize the extrapolation of efficacy data commented in the previous paragraph, tables 2 and 3 were elaborated based on the Guide for the Evaluation of Efficacy of additives produced by the European Food Safety Authority – EFSA, which brings the summary of physiologically related species and minimum number of studies for species and categories of target animals necessary to increase efficacy.

Table 2 - Extrapolation of efficacy data from species to other physiologically related ones.

| Species | Physiologically related species |
|---|---|
| Broiler chickens | Other broiler birds (turkey, duck, goose, quail, guinea fowl, ostrich, pheasant and others) |
| Laying hens | Other birds for egg production or breeding, but limited to the effects obtained on layers (turkey, duck, goose, quail, chicken d'angola, ostrich, pheasant and others) |
| Infant, weaned and porcine piglets in growth/termination | Other growing Suidae |
| Sows | Other Suidae in breeding |
| Calves and cattle for fattening | Other ruminants at the corresponding stage (sheep, goats and buffaloes) |
| Dairy cows | Other dairy ruminants (sheep, goat and buffalo) |

| | |
|---|---|
| Fish | Other fish of the same order and family taxonomic at the corresponding physiological stage. |
| Horses | Other equidae |
| Rabbits | Other leporids |

*Source: Adapted from the Guidance on the assessment of the efficacy of feed additives, EFSA, April 2018.*

Table 3 -. Minimum number of studies of target animal species and categories required for evaluation and enhancement of efficacy.

| Application to species/categories | Minimum number of studies per species/category |
|---|---|
| All species of poultry (chicken, turkey, duck, goose, quail, chicken d'angola, ostrich, pheasant and others) | 1 study with broilers |
| All species of broiler and breeding birds (chicken, layer, turkey, duck, goose, quail, chicken d'angola, ostrich, pheasant and others) | 1 study with broilers; and 1 study with layers |
| All growing/finishing pigs (piglet, growing/finishing pigs and other growing/finishing Suidae) | 1 study with weaned piglets; and 1 study with growing pigs |
| All pigs (piglet, growing/finishing pigs, sows and other growing/finishing Suidae and breeding) | 1 study with weaned piglets; and 1 study with sows |
| All growing ruminants (calf, fattening cattle and sheep or goats or growing buffaloes) | 1 study with calves; and 1 study with cattle for fattening |
| All ruminants (calf, cattle for fattening, cow and sheep or goats or buffaloes in growth and reproduction) | 1 study with calves; and 1 study with cows |
| All fish | 1 study with fish of the same order and taxonomic family; and 1 study with fish of another order and taxonomic family |
| Crustaceans | 1: study with shrimp or other crustaceans |
| Growing/fattening rabbits and reproduction | 1 study with growing rabbits; 1 study with rabbits in breeding |

*Source: Adapted from the Guidance on the assessment of the efficacy of feed additives, EFSA, April 2018..*

To prove the effectiveness will be accepted scientific publications or by own experimentation in Portuguese, English or Spanish, provided that these are the languages of the original texts, but in other languages must be translated simple into Portuguese or English or Spanish.

The reports of the efficacy studies should contain at least: title, approval in the ethics committee, abstract, objective, material and methods (location, climatic conditions, age and breed/lineage of the animals, diets, treatments, parameters evaluated, management, experimental design, statistical methods, analytical methods, etc.), results, discussion, conclusion and literature cited.

The full application of the requirements contained in this topic will occur after 24 months of the publication of this roadmap, however efficacy studies continue to be necessary for the registration of additives, and should contain at least methodology, statistical analysis of the data and be in full and in Portuguese or English or Spanish.

### 2.12. Additional requirements for imported products

In addition to the above requirements, it will be necessary to present the following documents:

1. Legal document, issued by the owner established abroad, that enables the representative in Brazil to answer to the Ministry of Agriculture, Livestock and Supply for all regulatory requirements, including any infractions and penalties and other obligations arising from the registration of the product;

2. Certificate of official qualification of the establishment owner and manufacturer in the country of origin;

3. Official certificate of registration or authorization of free sale or even of the exclusive manufacturing authorization for export of the product in the country of origin, specifying the composition;

4. A declaration issued by the competent authority of the country of origin or by an assessment body officially accredited in the country of origin that the establishment complies with good manufacturing practice;

5. Copy of the original label of the country of origin.

The documents containing the validity period must be in force at the time of the registration request.

## 2.13. Renewal of registration

The company must submit a self-declaration signed by the Responsible Technical containing the following topics:

a) on the composition and purity or activity in relation to the registered product;

b) on the safety of the additive in relation to the conditions approved for target species and animals, consumers, workers and the environment;

c) on possible harmful effects on target species and animals, consumers, users and the environment;

d) about possible interactions and cross-contamination previously unknown.

Finally, you should attach the report of the long-term stability study, when it is pending at the time of registration.