

# **Comparison of Approval Process and Risk-Assessment Procedures for Feed Ingredients**

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Feed Additive Comparison Project Task Force**

## **PREAMBLE**

For the past 3 years, IFIF has hosted an annual meeting with feed regulators from several global regions, focused on addressing common issues and providing insight into each of the represented regions' feed regulatory processes. Following the 2010 meeting, IFIF undertook this comparison project to identify the commonalities and differences in the risk-assessment and approval processes for feed ingredients, which ultimately affects the ease of trade of feed and ingredients among these regions. It is the expectation that this report will provide the industry with an understanding of requirements for the compared categories of feed ingredients in each region and also serve as a reference for regulators to work toward a better harmonization or equivalency of regulatory approaches among the regions.

## **OBJECTIVE**

To compare the approval process and risk-assessment procedures as related to feed additives or feed ingredients for three regulatory jurisdictions: the United States of America, Canada, and the European Union.

## **EXECUTIVE SUMMARY**

This report compares the approval processes for feed ingredients for three regulatory jurisdictions: the United States of America (US), Canada, and the European Union (EU). Most new feed ingredients (defined as feed additives in Europe, single ingredient feeds in Canada, and food additives in the United States) are subject to premarketing authorization in the three jurisdictions, and submissions cover the safe manufacture, the safety of the ingredient to the target animal and the human consumer, and the efficacy or utility of the ingredient. In all three regulatory jurisdictions the submission requirements vary as related to composition of the new additive, intended use, species, and the method of manufacture.

The type of information required for authorization (or registration) of a new feed additive or ingredient by the regulatory jurisdictions is best understood by review of Table 2 in the report. The United States and European Union regulations describe a category of feeding materials that do not need to be authorized prior to marketing (see Table 1), whereas in Canada all ingredients used in livestock feed must be a part of the Feed Regulations schedules IV or V. Canada only regulates livestock feed (see Appendix 1 for definition), whereas the US and EU regulate feed intended for all animals.

Each regulatory jurisdiction requires the submission of information on the intended use (function) of the feed ingredient. There are differences among the regulatory jurisdictions as to what intended use can be ascribed to feed (see Table 3). The EU has defined specific categories and subcategories appropriate for feed additives. In the US and Canada, significant decisions on the regulation of feed substance (feed vs. drug) are made based on the intended use of the ingredient. The most significant differences are for animal production claims, coccidiostats, and histomonostats. The US regulates all products that are intended for increased animal production or to diagnose, prevent, treat or mitigate diseases as animal drugs. Canada permits certain feed ingredients to have animal-production claims, but all products intended for the diagnosis, prevention, treatment or mitigation of diseases -- including salmonellosis and gut-flora stability (probiotics and prebiotics) -- are regulated as animal drugs. The EU permits feed additives that function as performance enhancers and that prevent coccidiosis and histomonosis (category 4 and 5 feed additives).

The EU has specific regulations that describe the requirements for feed additives manufactured using genetic modification, and it requires specific identification labeling and post-marketing plans. The US has no specific regulation of ingredients manufactured using genetic modifications. Both the US and Canadian approach is product- rather than process-based. Canada has specific guidance for products of biotechnology, both plant and microbial sources, and is currently revising Chapter 2 of their Regulatory Guidance 1 to update the guidance for this category of feed. In the US feed ingredient listings are generally non-proprietary; once a product is listed others can base their marketing on this listing. The EU considers categories 1, 2, and 3 feed additives non-proprietary; however Category 4 (zootechnical) and Category 5 (coccidiostats and histomonostats) are specific for the authorization-holder. Feed ingredients listed in Part 2 of Canada's schedules IV and V feed-ingredient listing are specific to the registrant.

Although each jurisdiction's submission requirements vary with the type of ingredient (e.g. intended use, species, chemical composition; see Table 4) there is minimal guidance as to what the specific submission requirements are in the US and Canada. This allows flexibility to consider a wide range of studies, but it also causes uncertainty for the feed industry to not have a specific understanding of what will be expected by the regulators. Canada addresses this issue with Regulatory Guidance 1, which is continually being updated to ensure it provides current information.

### **INTRODUCTION**

For practical reasons, the scope of this comparison project was limited to three regions: US, Canada and the EU, with the understanding that this comparison can be expanded in a future phase. Brazil served as an observer in this project. The analysis was developed with the knowledge and expertise of an expert team from each region, including feed regulators (FDA, CFIA, EC) and industry experts AFIA, ANAC, FEFAC, FEFANA, Sinderacios).

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Each of the three regulatory jurisdictions has its own approval process and terminology for substances that are used to make up an animal feed. It is the intent of this report to consider all substances that are used in the manufacture of feed for animals. In some instances terms in one jurisdiction mean something quite different in another jurisdiction. Appendix 1 provides the regulatory definition of all three regulatory jurisdictions and should be used as a reference in understanding this report. The CODEX definitions are included as a point of reference.

Each regulatory jurisdiction uses its own terminology for feed ingredients and those terms differ from the Codex definitions (see Appendix 1 for a full listing of defined terms). This difference in terminology affects how each region classifies and regulates these substances. The following comparison is important for recognizing how each region defines and regulates various categories of feed ingredients.

	<b>CODEX</b>	<b>US</b>	<b>CAN</b>	<b>EU</b>
Ingredient	Feed ingredient	N/A	Single Ingredient Feed	N/A
Feed Substance Not Requiring Authorization	N/A	Common Food	N/A	Feed material
Additive	Feed additive	Food additive	N/A	Feed additive
Drug	Veterinary drug	Animal Drug	Veterinary Drug	Veterinary animal product
GRAS	N/A	GRAS	N/A	N/A

(See Table 1 for a full explanation)

The report focuses on all “feed ingredients” that require some authorization or regulatory review through the typical processes used in the United States (animal Food Additive Petitions, Generally Recognized As Safe determinations, and AAFCO-defined products); Canada (Single Ingredient Feed Registration); and the European Union (Feed Additive Applications). For this report the term feed ingredient is used as a generic term cover all the feed substances as regulated by the three jurisdictions, not a legal terms specific to any one regulatory body.

The comparison identifies and describes the main regulatory process and risk assessment that is applied to this range of ingredients in each regulatory jurisdiction. It draws on the established laws, regulations, and guidances offered by each regulatory jurisdiction. A reference section provides internet links to all the references used. However, for some areas of the report, personal interviews from the regulatory officials or people in the regulated industry were necessary to complete the comparison.

In all regulatory jurisdictions substances that may be added to feed include items that are regulated as animal drugs (veterinary health product, veterinary drugs, etc). Each regulatory jurisdiction defines these products differently; however, the scope of this

report is to identify those areas in which feed ingredients overlap with another regulatory jurisdiction's drug products, not to define the regulatory process for drug approvals or compare those procedures.

In addition, this report relies on many regulatory acronyms that are defined in Appendix 1. A listing of products that are prohibited for use in animal feed can be found in Table 5.

All jurisdictions have regulatory requirements and different inspection programs covering the use of the feed ingredients (for example feed mill inspection) to assure safety of the feed for livestock. These requirements and inspection programs are outside of the scope of this comparison.

### **BACKGROUND**

In all three jurisdictions there are a number of feed substances that do not require an additional regulatory review process because they are either exempt from the process or they have been previously authorized. The feed substances that can be marketed in each regulatory jurisdiction are listed in Table 1.

The European Union feed materials do not require premarketing authorization. Generally these materials are defined as “products of vegetable or animal origin, whose principal purpose is to meet animals’ nutritional needs, in their natural state, fresh or preserved, and products derived from the industrial processing thereof, and organic or inorganic substances, whether or not containing feed additives, which are intended for use in oral animal-feeding either directly as such, or after processing, or in the preparation of compound feed, or as carrier of premixtures.” There is, however, a system of notification, via the Register of Feed Materials, for those that are placed on the market for the first time after September 1, 2010. The EU has a nonexhaustive, nonbinding list of feed materials that was established only for labeling purposes. It is the responsibility of the feed-material producer to assure feed materials are safe for use. No products are exempt based on previous use (history of use). Feed additives listed in categories 1-3 on the EC Community Register of Feed Additives appendices 3 and 4 can be used as a basis to market additives and are not holder-specific authorizations. Feed additives listed as categories 4 and 5 are holder-specific authorization, so they can be marketed only by the person that sponsored the establishment of the authorization

The Canadian regulations provide a listing of all permitted feed ingredients in the Feeds Regulations schedules IV and V. Each of these schedules has two parts. Ingredients listed in Part 1 are non-proprietary feed ingredients and the listing can be used by anyone for the basis of marketing. Feed ingredients listed in Part 2 are specific to the registrant and can only be marketed by the registrant once they are registered.

The United States regulations (21 CFR 582.1(a) and 21 CFR 573.20(d)) state that there is not a listing of all permitted ingredients and that some ingredients of natural biological origin are acceptable feed ingredients (Table 1). In addition, the FFDCA law permits

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self-determination of Generally Recognized As Safe ingredients (FFDCA 201(s)), so that any person can establish the safety of such a feed ingredient and market that ingredient. Feed Ingredients defined in the American Association of Feed Control Officials Official Publication can be used as a basis for marketing, as well as those feed additives listed in 21 CFR 573, ingredients grandfathered as GRAS listed in 21 CFR 582, and determination affirmed as GRAS by the FDA as listed in 21 CFR 584.

The parameters that are part of and/or taken into account in the respective risk-assessment processes of the US animal Food Additive Petitions and Generally Recognized As Safe determinations, Canadian Single Ingredient Feed Registration, and the European Union Feed Additive Authorization are summarized in Table 2.

### Regulatory Processes Available for Feed Ingredients

US	Canada	EU
<p><b><u>Common Food</u></b>            -- No premarket approval</p> <p><b><u>Food Additive</u></b>            -- Premarket approval required            -- Full safety and utility assessment required            -- All codified food additives are non-proprietary</p> <p><b><u>GRAS Determination</u></b>            -- No pre-market approval required            -- Safety assessment must rely on published data and be held by supplier            -- Determination must be specific to an intended use</p> <p><b><u>GRAS Determination With FDA Notification</u></b>            -- Submission of determination to FDA for review            -- FDA review is specific to the notifier</p> <p><b><u>AAFCO DEFINITION</u></b>            -- AAFCO/FDA review of the safety and utility assessment            -- Ingredient definition is non-proprietary</p>	<p><b><u>Single Ingredient Feed</u></b>            -- Premarket approval required            -- full safety and efficacy assessment required            -- Positive list (proprietary or non-proprietary, depending on part)</p>	<p><b><u>Feed Material</u></b>            -- No premarket approval required            -- Supplier must have safety and efficacy on file            -- Negative list</p> <p><b><u>Feed Additive</u></b>            -- Premarket approval required            -- Application to Evaluation Commission            -- Risk assessment by EFSA            -- Positive list by target species (proprietary or non-proprietary, depending on category)</p>

**SAFETY ASSESSMENT/APPROVAL PROCESS**

In each of the regulatory jurisdictions new feed ingredients for livestock feed (and companion animal feed in the US and EU) must be demonstrated to be safe and effective for the intended use prior to marketing the ingredient. The safety assessment must include safety to the target species as well as human food safety for the milk, meat and eggs produced by the livestock. However, there are differences in the approach to the safety assessment and what ingredients must be evaluated using this process. Each regulatory jurisdiction outlines its process in the regulations specific for that jurisdiction. Canadian officials also rely on Regulatory Guidance 1 (currently under development) to provide further interpretation of the requirements. EU regulations (Commission Regulation (EC) No 429/2008) are structured such that the regulation describes the administrative and general scientific requirements of an application requesting authorization of a new feed additive; then the regulation continues with specific data requirements for each category of feed additives, as provided in Annex III: Specific Requirements to Be Satisfied by the Dossier Provided For In Article 3 With Respect to Certain Categories of Additives or Certain Particular Situations. Although there is a single process (with varying data requirements) for registering a new feed ingredient in Canada (single ingredient feed registration), as well as a single authorization process in the EU, there are multiple avenues to legally market a new feed ingredient in the US.

The US food and drug laws and regulations permit self-determination of Generally Recognized As Safe as a legal process. However, generally liability issues and the state's unwillingness to register a feed ingredient that does not have an FDA or AAFCO listing have made this procedure rare. Filing a Food Additive Petition (21 CFR 571.1) results in a food additive regulation describing the use and specifications for the food additive. The law also provides for the filing of petitions to request FDA affirmation of Generally Recognized As Safe (21 CFR 570.35), resulting in a regulation of an affirmed GRAS ingredient, but the agency has phased out this procedure. General recognition of safety through scientific procedures requires the same quantity and quality of scientific evidence as is required to obtain approval of the substance as a food additive and ordinarily is based upon published studies, which may be corroborated by unpublished studies and other data and information. The FDA interprets GRAS as for an intended use; therefore, the intended use must also be supported. Under the newly adopted pilot procedures (75 FR 31800) the FDA will review GRAS determinations through a notification procedure; however, the FDA has suggested that this procedure is specific to the notifier, unless another person makes a separate determination of safety of the ingredient. Historically the FDA has also worked with the American Association of Feed Control Officials in establishing definitions for new feed ingredients (see FDA-AAFCO MOU). This process was completed under regulatory enforcement discretion, in which the FDA responded in letters indicating that it had "no objections" to the establishment of a new or revised feed ingredient definition. However, at the AAFCO 2010 Annual Meeting Ingredient Definition Committee meeting, Sharon Benz, on behalf of the FDA, stated that it is phasing out its support of the AAFCO definition process (see IDC meeting notes).

Within this task force report, reference to the FDA regulation of food additives is intended to cover all premarket review standards currently permitted by the FDA, as it is the FDA's intent to "require the same quantity and quality of scientific evidence" whether evaluated under the GRAS notification or the food additive petition process (75 FR 31800).

The US regulations are very broad, and further interpretation of the regulations is provided either in open meetings or in individual industry meetings. There are a few specific FDA guidances available for the evaluation of safety and utility of food additives or feed ingredients (see reference listing); however, the agency also relies on available animal drug guidance for the safety assessment.

Table 2 outlines the requirements for a typical animal feed ingredient that needs to be evaluated by each regulatory jurisdiction. The table is heavily referenced to permit ease of determination of specifics of that regulatory approval process.

### **DIFFERENCES AMONG REGULATORY JURISDICTIONS**

This section provides an evaluation of the differences among the regulatory approaches of each jurisdiction. Table 3 of the report gives an overview of the type of claims or function of a feed ingredient and how each jurisdiction regulates such a product. Table 4 details some specific products and the regulation of those products in each jurisdiction. Below significant differences are described under broad headings.

**ANIMAL SPECIES-COMPANION ANIMALS:** The US and EU regulate feed ingredients intended for use for all animal feed. The Canadian feed ingredient evaluation process is specific to livestock, defined as horses, cattle, sheep, goats, swine, foxes, fish, mink, rabbits and poultry. There are no approval requirements for feeds or single ingredient feed for non-livestock species. The US requirements for evaluation of food additives intended for use in companion animals are quite rigorous and, if intended for broad use (in feeds labeled as "complete feeds"), the requirements include studies to demonstrate safety following animals from pre-gestation, gestation, lactation, and growth of young. The EU will waive tolerance (safety) testing if the ingredient is approved for use in three major species (see Table 4 and Appendix 1).

**ANIMAL SPECIES-MINOR SPECIES:** The EU defines minor species as food-producing animals other than bovines (dairy and meat animals, including calves), sheep (meat animals), pigs, chickens (including laying hens), turkeys and fish belonging to the Salmonidae ((EC) No 429/2008). The US defines minor species as animals other than cattle, horses, swine, chickens, turkeys, dogs, and cats (MUMS Act, 2004). Canada does not use the terminology of minor vs. major species, but defines livestock (see description above). The significance of these definitions is that in the EU the submission requirements for minor species are generally more limited. Tolerance studies for minor species are not required if the additive showed a wide margin of safety (at least a factor of 10) in the relevant physiologically similar major species; if three major target species

(including monogastric and ruminant mammals and poultry) showed a similar and wide margin of safety, no additional tolerance studies would be required for non-physiologically similar minor species (e.g. horses or rabbits). In addition efficacy studies would be waived when an additive is already approved for a physiologically comparable major species for the same function and, where the mode of action of the additive is known or demonstrated, evidence of the same mode of action in the minor species can be taken as evidence of efficacy (EC 429/2008 Chapter 6 Extrapolation From Major to Minor Species). For the US there is no distinction in regulation or guidance for feed additives intended for minor or major species, except in the case of utility requirements for products intended for use in aquaculture (GFI 80) that provide very specific guidance on study design to support the utility section of the petition. Upon consultation with the FDA certain provisions for feed additives intended for minor species may be granted. Also in the US, some ingredients (recently this is very limited) may be cleared for use by animals (defined as “all animals”), including all major and minor species, and generally those submissions are based on data collected for major species. Canada has no registration requirements for feed or feed ingredients intended for use in non-livestock species.

**ANIMAL PRODUCTION CLAIM OR FUNCTION:** One of the most significant differences in the regulation of feed ingredients is related to identification of function of the ingredient to increase the production of meat, milk and eggs. In the US, the FDA has “traditionally reserved claims for improving animal production, such as increased milk production, increased leanness, and improved growth and efficiency of gain, to drugs. These claims will not be permitted for animal feed and nutritional ingredients.” (FDA P&PG 1240.3605). Therefore, feed additive submissions cannot be based on an intended use (utility) to increase in animal production.

In Canada, the guidance covering live microbials/yeast and yeast cell wall products (RG1, chapter 3.22 and 3.23) specifically states that these products with claims within the normal range can be regulated as feed. Guidance specifically discusses claims of “improvement of appetite, weight gain, feed efficiency and other production parameters to within normal ranges as defined in current National Research Council (NRC) or equivalent published literature, under normal conditions of animal husbandry. In the absence of NRC published values, the inclusion of a positive control group in an efficacy trial as a reference standard would be acceptable. Normal conditions of animal husbandry may include weaning, ration changes, vaccination, debeaking, dehorning, castration, shipping, etc.” Improvements of production parameters beyond normal would be considered a drug and would be regulated under Part C, Division 8 of the Food and Drug Regulations. Communications with the CFIA staff indicated that this same criteria may be used for other feed ingredients, but at this time it is restricted to viable microorganisms and yeast cell wall products

The EU defines zootechnical additives (Category 4 Feed Additives) as “any additive used to affect favorably the performance of animals in good health or used to affect favorably the environment” ((EC) No 1831/2003, Article 6). Zootechnical additives have function

as defined as “(a) digestibility enhancers: substances which, when fed to animals, increase the digestibility of the diet, through action on target feed materials; (b) gut-flora stabilizers: microorganisms or other chemically defined substances, which, when fed to animals, have a positive effect on the gut flora; (c) substances which favorably affect the environment; (d) other zootechnical additives ((EC) No 1831/2003, Annex 1). Therefore, zootechnical additives can have a described function of enhancing production.

### **FEED INGREDIENTS PRODUCED THROUGH BIOTECHNOLOGY OR GMOs:**

The EU has specific regulations that cover ingredients manufactured through genetic modification ((EC) No 1829/2003 and 1830/2003). In addition the EU has both identification labeling and post-marketing plans required for these products, and some in the industry believe these provisions have impeded the adoption of biotechnology in feed production. The US FDA has an effective Premarket Biotechnology Notification, required prior to marketing plant crops or other ingredients derived from altered plants for food or feed. Although written guidance is not available, the FDA also regulates food additives produced by GMOs similarly to other food additives, with special consideration to the unintended effects of gene transfer and the release of GMOs to the environment. Canada has specific guidance for the application for the authorization of the release of a novel feed (biotech plants) and also has specific guidance as related to feed produced through GMOs, but this guidance is currently being updated (RG1; Section 2.6). Canada requires an environmental assessment for all novel products or new feeds with novel traits. The Canadian regulatory system for biotechnology products is product- rather than process-based. As a result, Canada has adopted a very broad definition of biotechnology and has focused regulations on novel traits or “new” organisms rather than “genetic engineering” itself. The FDA has a similar approach where the safety of the product is assessed, and specific regulations are not required for products manufactured through biotechnology.

**SAFETY STUDIES:** The EU regulations require prescribed safety studies that are used to support the feed additive submission (target animal safety, human food safety, worker safety, and environmental safety). Annex III of the regulations (EC 429/2008) provides specific guidance to the studies required and the duration of the studies. If target animal safety is to be addressed, tolerance studies are used. Canada relies mostly on mammalian toxicology tests (acute and chronic) to support the human food safety and target animal safety assessment. Specific guidance on the required studies to support FDA submission for specific feed additives is not provided, but when studies are required FDA often relies on the animal drug guidance. FDA does not rely on acute or dermal toxicology studies when assessing safety and does not rely on tolerance testing to support target animal safety. US target animal studies are generally conducted from weaning to market weight at 0, 1X, 3X, and 5X the intended use level. Studies to support use in companion animals generally include pre-breeding, gestation, lactation, and growth (young).

**ENVIRONMENTAL ASSESSMENTS AND WORKER SAFETY:** The EU requires an environmental assessment and studies to demonstrate worker safety for all applications for new feed additives. The US FDA requirement for environmental

assessment is based on the regulatory approach for the food additive. All Food Additive Petitions (and animal drug applications) require an environmental assessment; neither the AAFCO Definition Process nor the GRAS notification process requires environmental assessments. The FDA does not require any specific studies to demonstrate worker safety for food additives; however, if there is a particular concern, the FDA can ask for data to support appropriate labeling or regulation. In addition labeling can reflect information on the MSDS. Based on input from the Canadian-regulated industry and CFIA officials it was unclear whether all feed registrations for new single ingredient feeds require an environmental assessment or if only novel food or feed ingredients with novel trails require submission of an environmental assessment. The *Feeds Regulations* require satisfactory evidence to support the safety of the feed in respect to livestock and its potential effect on humans and the environment. The amount of information is dependent on the use of the product,

**SALMONELLA-CONTROL AGENTS:** The FDA considers products intended to “maintain feed salmonella-negative” to be food additives and provides specific guidance as to how to demonstrate those claims (FDA, GFI 80). Products intended to treat salmonellosis would be considered animal drugs. In Canada, salmonella-control agents used in the feed are regulated under Health Canada’s Veterinary Drug Directorate. CFIA allows mold inhibition claims as feeds, not salmonella control. Canadian feed industry representatives indicate that carefully crafted anti-salmonella claims may be considered feeds. The EU regulates additives that function as preservatives as technological additives (see Table 4).

**PROBIOTICS/PREBIOTICS:** In Canada, probiotics and prebiotics used in the feed are regulated under Health Canada’s Veterinary Drug Directorate. Canadian feed industry representatives indicate that carefully crafted probiotics and prebiotics claims can be considered feeds. The EU regulates feed additives that function as digestibility enhancers or gut-flora stabilizers as zootechnical additives (see Table 4). Under the newly issued FDA guidance on complementary and alternative medicine, probiotics and prebiotics can be regulated as food additives or an animal drug, depending on intended use.

**FLAVORS:** The EU exempts non-processed botanicals from requiring authorization as a feed additive. Processed natural flavors and artificial flavors are feed additives. The US FDA permits all natural flavors as listed in the human GRAS and food additive regulations to be used as flavors in animal feed without further review. Canada has no global exemption for botanical flavors in their regulation or guidance; all new flavors must be registered as a new single ingredient feed. See Table 4 for further information.

**FEED INGREDIENTS INTENDED TO DIAGNOSE, PREVENT, MITIGATE OR TREAT DISEASE, INCLUDING COCCIDIOSIS AND HISTOMONOSIS:** Canada and the US regulate all products that are intended to diagnose, prevent, treat or mitigate diseases in animals as a drug. Drug approvals for these products are required prior to marketing. Canada also regulates most products to treat salmonellosis and to serve as probiotic and gut-flora stabilizers as animal drugs. The US regulation of anti-salmonella

agents and probiotics and prebiotics are regulated as a food additive or drug based on the specific intent (effect on the feed vs. effect on the animal). The EU allows products that function as coccidiostats and histomonostats to prevent disease, to be regulated as feed additives (Category 5); feed substances intended to diagnose, prevent, treat or mitigate other diseases are regulated as veterinary pharmaceuticals.

**PROPRIETARY NATURE OF FEED INGREDIENTS:** The EU categories 4 (zootechnical) and 5 (coccidiostats and histomonostats) feed additives are holder-specific authorization, and as such can only be marketed by the person submitting the authorization application. In Canada schedules IV and V listing of feeds have two parts each. Single ingredient feeds listed in Part 2 are proprietary approvals. CFIA determines which feeds are listed in Part 2 based in part on the consistency of manufacture, safety considerations, and proprietary analytical methods. The US FDA establishment of Food Additive Regulations and AAFCO Ingredient Definitions are non-proprietary, and anyone that meets the specifications of the ingredient can market under these regulations and definitions. Because of the nature of GRAS notifications -- determinations made by the manufacturer for a product it manufactures or uses -- they are specific to the notifier. However, as the self-determination of GRAS status is a legal means to market, it is unknown whether other feed ingredient manufacturers will submit GRAS notifications for their self-determination for a feed ingredient or refer to the previously issued "no question at this time" letter. At this time the FDA has not made public the filing of any GRAS notifications nor any determinations of the acceptability of a GRAS notification.

**SPECIFIC SUBMISSION REQUIREMENTS FOR FEED INGREDIENTS:** Table 2 reviews the general submission requirements for authorization to market a new feed ingredient. Table 4 provides the requirements for specific examples of feed ingredients. In all three regulatory jurisdictions the submission requirements vary as related to composition of the new additive, intended use, species, and the method of manufacture. In the EU differences in submission requirement are provided in regulations ((EC) 429/2008) for specific categories and function groups. However, the definition for feeding material and feed additive include some overlap, and decisions on requiring a feed additive submission may be determined by the function for the specific ingredient. The recent adoption of EC 767/2009, which describes feeding materials and does not provide a listing of feeding materials, has introduced some ambiguity. Also, the decision that all feed additives currently marketed were required to submit a re-registration by November 7, 2010; has stressed the system, such that the evaluation of these submissions will take 4-5 years.

Canadian Feed Regulations and the US FDA's regulation (21 CFR 571.1) are rather perfunctory documents that only provide the most general framework to demonstrate the safety and utility of the new ingredients. These regulations were established many years ago, and both groups have found that the lack of specific regulations allows them to be very flexible as to what is required, without requiring a set of specific tests. This allows the regulators to examine a number of types of studies to complete the package. The animal feed industry appreciates the flexibility; however, when starting a new project or

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if a company is new to the feed ingredient area, the lack of specific guidance can be daunting. Some have suggested the flexibility can lead to moving targets and an issue of differences in interpretation between reviewers within the review division. Canada has recently begun tackling this issue with the establishment of Regulatory Guidance 1, which provides specific guidance on a number of specific categories of feed ingredients. This guidance is being established with public participation. The US has few specific feed additive guidances available. There is little information available covering the regulation of specific categories of feed ingredients. The feed industry must rely on meetings with FDA, shared experiences from others or consultants, and FDA or feed industry PowerPoint presentations sometimes available online from conference proceedings (see the reference list for examples). The extensive process the FDA requires to issue a new guidance inhibits the ready adoption, publication, and modification of guidance.

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### **ATTACHMENTS:**

**TABLE 1: FEED INGREDIENTS THAT CAN BE MARKETED WITHOUT FURTHER REVIEW/AUTHORIZATION**

**TABLE 2: INFORMATION REQUIRED IN THE SAFETYASSESSMENT / RISK ASSESSMENT PROCESSES**

**TABLE 3: PERMITTED INTENDED USE OR FUNCTION FOR FEED INGREDIENTS**

**TABLE 4: IDENTIFICATION OF REGULATORY PROCESSES THROUGH TYPICAL NEW INGREDIENT EXAMPLES; WITH SPECIFIC REGULATORY GUIDANCE**

**TABLE 5: PROHIBITED SUBSTANCES IN ANIMAL FEED**

**APPENDIX 1: ACRONYMS and DEFINITIONS**

**APPENDIX 2: FEED ADDITIVE CATEGORIES: REGULATION (EC) No 1831/2003, ANNEX I**

### **REFERENCES**

TABLE 1. FEED INGREDIENTS THAT CAN BE MARKETED WITHOUT FURTHER REVIEW/AUTHORIZATION

Category	US	Canada	EU
<p>Grains/Typical Feed Ingredients/Feed Materials (that have not previously undergone review /authorization)</p>	<p>-- Common food ingredients (21 CFR 582.1(a)).                      --A food ingredient of natural biological origin that has been widely consumed for its nutrient properties in the United States prior to January 1, 1958, without known detrimental effects, which is subject only to conventional processing as practiced prior to January 1, 1958, and for which no known safety hazard exists, will ordinarily be regarded as Generally Recognized As Safe (GRAS) (21 CFR 570.30(d))                      -- Substances that have been determined to be safe by self GRAS determination (FFDCA 201(s) and CFR 570.30(a))</p>	<p>None. Canada has a positive list of ingredients. Only ingredients listed in schedules IV or V, part I, of the federal Feeds Regulations may be used without further review or approval .</p>	<p>--<sup>1</sup>Feed materials are not regulated as feed additives and do not require premarket review.                      -- A nonbinding, nonexhaustive list of feed material defined as the “Community Catalogue for feed materials” (Regulation 767/2009), first catalogue published in Regulation 242/2010.                      -- Feeds materials placed for the first time on the market after September 1, 2010, must be published in the EU register. (It is not a pre-marketing authorization, but just a “notification.”)                      -- Feed materials that are GMOs require a pre-marketing authorization. (Regulation 1829/2003)                      -- Feed materials are primarily used to meet animals’ needs, for example for energy, nutrients, minerals or dietary fibers. They are usually not chemically well-defined except for basic nutritional constituents. Effects that can be justified by scientific assessment and that are exclusive to feed additives or veterinary drugs should be excluded from the objective uses of feed materials. The Commission may draw up nonbinding guidelines for distinguishing between these kinds of products (in the process of publication at present, together with the catalog of feed materials).                      -- Where there are no specific European Community provisions, feed shall be deemed to be safe when it conforms to the specific provisions of national law governing feed safety of the member state in whose territory the feed is in circulation, such provisions being drawn up and applied without prejudice to the treaty, in particular Articles 28 and 30 thereof. (EU REGULATION (EC) No 178/2002, article 15)</p>

TABLE 1. FEED INGREDIENTS THAT CAN BE MARKETED WITHOUT FURTHER REVIEW/AUTHORIZATION  
(Continued—page 2)

Category	US	Canada	EU
<p>Substances that have undergone review or authorization</p>	<ul style="list-style-type: none"> <li>-- Food additives currently listed in 21 CFR 573: Food Additives Permitted in Feed and Drinking Water of Animals</li> <li>-- Feed substances that were recognized as safe prior to 1958 and listed in 21 CFR 582: Substances Generally Recognized as Safe (GRAS)</li> <li>-- Substances that were affirmed by the FDA as being GRAS. 21 CFR 584: Food Substances Affirmed as Generally Recognized as Safe in the Feed and Drinking Water</li> <li>-- Substances self-determined to be GRAS with Notification to FDA: Proposed Rule:75 FR31800; June 4, 2010</li> <li>-- Feed ingredients whose use has been defined and published in the AAFCO Official Publication and that meet the definitions.</li> <li>-- Drugs (proprietary) that have been approved for specific use in animal feed. 21 CFR 558: New Animal Drugs For Use in Animal Feeds</li> </ul>	<p>Canada has a positive list of ingredients. Only ingredients listed in schedules IV or V, part I, of the federal Feeds Regulations may be used without further review or approval.</p>	<p>–EU authorizations are compiled in the Community Register of Feed Additives pursuant to Regulation (EC) No 1831/2003. Feed additives listed in categories 1, 2, and 3 can be used as a basis of marketing. Feed Additives listed as categories 4, 5, and GMOs are specific to the authorization holder (proprietary).</p>

TABLE 2: INFORMATION REQUIRED IN THE SAFETY ASSESSMENT/RISK ASSESSMENT PROCESSES

Concern	USA <sup>1</sup> (food additive)	CANADA <sup>2</sup> (feed ingredient)	EU <sup>3</sup> (feed additives)
<b>SAFETY</b>	<p>Safe or safety means that there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use. It is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of the use of any substance. Safety may be determined by scientific procedures or by general recognition of safety. In determining safety, the following factors shall be considered:</p> <p>(1) The probable consumption of the substance and of any substance formed in or on food because of its use.</p> <p>(2) The cumulative effect of the substance in the diet, taking into account any chemically or pharmacologically related substance or substances in such diet.</p> <p>(3) Safety factors which, in the opinion of experts qualified by scientific training and experience to evaluate the safety of food and food ingredients, are generally recognized as appropriate. (21 CFR 570.3(i))</p> <p>Target animal safety and human food safety must be addressed in all new submissions. Environmental safety must be addressed only in Food Additive Petitions (FAP) and NADAs.</p>	<p>All feeds must be safe for animals and humans (food safety and worker/ bystander safety), and the environment. As per section 3.(3) of the Feeds Act: No person shall manufacture, sell or import into Canada in contravention of the regulations any feed that may adversely affect animal or human health. The Canadian approach to the safety assessment is a weight of evidence approach; the specific requirements for a new ingredient may vary depending on the nature of the ingredient.</p> <p><b>Safety Information</b> (as necessary) Scientific investigations concerning, but not limited to, chemical analyses and/or harmful residues and/or toxicological evaluation and/or animal feeding study and/or tissue residue analysis etc. presented in support must be:</p> <ul style="list-style-type: none"> <li>-- Carried out by qualified research personnel.</li> <li>-- Carried out using suitable methods.</li> <li>-- Designed to facilitate statistical analysis.</li> <li>-- Analyzed by appropriate statistical methods.</li> <li>-- Conducted under conditions similar to those that may be expected to occur in Canada. (RG1, chapters 2.3 and 2.4)</li> </ul>	<p>Feed additives shall not have an adverse effect on animal health, human health or the environment (Art 5, Reg 1831/2003) Safety is based on studies intended to demonstrate the safety of the use of the additive in relation to:</p> <p>(a) The target species at the highest proposed levels of incorporation in the feed or water.</p> <p>(b) Consumers who ingest food products obtained from animals that have received the additive, its residues or its metabolites. In this case, safety will be ensured by the setting of maximum residue limits (MRLs) and withdrawal periods. MRLs may be based on an Acceptable Daily Intake (ADI).</p> <p>(c) Persons likely to be exposed to the additive by respiratory, mucosal, eye or cutaneous contact while handling the additive or incorporating it into premixtures or complete feed or water or using feed or water containing the additive concerned.</p> <p>(d) Animals and humans with respect to the selection and spread of antimicrobial resistance genes.</p> <p>(e) The environment, as a result of the additive itself or products derived from the additive, either directly and/or as excreted by animals. Where an additive has multiple components, each one may be separately assessed for consumer safety, then consideration may be given to the cumulative effect (where it can be shown that there are no interactions between the components). Alternatively, the complete mixture shall be assessed. (EC) No 429/2008 Target animal safety, human food safety, environmental safety and worker safety are all covered in the safety documentation for new authorizations.</p>

TABLE 2: Information required in the safety assessment/risk assessment processes (continued)

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Concern	USA <sup>1</sup> (food additive)	CANADA <sup>2</sup> (feed ingredient)	EU <sup>3</sup> (feed additives)
<p><b>Target Animal Safety</b></p>	<p>General use of the FDA/CVM pharmaceutical guidance: Guideline 33 Target Animal Safety Guidelines For New Animal Drugs, 1989</p> <p>When currently available data is not persuasive to the determination of target animal safety FDA will require a safety study conducted under GLPs (or equivalent OECD) that meets the guidance such as a 0, 1X, 3X, and 5X dose study where toxicology-endpoints are assessed (CVM GFI 33(1998), 21 CFR 571.1)</p> <p>Companion Animal Safety requires reproduction and growth studies in the target species at multiple levels of exposure.</p>	<p>Mammalian toxicological data and pertinent livestock toxicity data are referenced for both target animal and human safety</p> <p>Data requirements as listed in RG-1, Ch. 2.3, 2.4, 2.5, 2.6, and/or 2.7 (depending on the nature of the ingredient)</p>	<p><b>Tolerance studies for the target species</b></p> <p>Tolerance tests must be conducted to provide evidence for safety for each of the target species/animal categories for which an application for authorization is made. Tolerance studies provide an evaluation of toxicity of the additive to the target animals and are used to establish a margin of safety, if the additive is consumed at higher doses than recommended. Tolerance studies may be combined with efficacy studies.</p> <p>The main characteristics of the tolerance studies to be carried out (dosages, duration etc..) are established in Regulation 249/2008.</p>
<p><b>Human Food Safety</b></p>	<p>Human food safety is required to be addressed for all substances intended for use in food-producing animals. If an understanding of safety based on currently available data is not sufficient a series of toxicological, metabolic and residue studies may be requested (this is typical for animal drugs). In addition FDA will request consideration of antimicrobial resistance issues in the feed and the GIT (for known antimicrobials).</p> <p><b>Metabolism Studies In Target Animals</b></p> <p>Metabolic fate of the compound in the edible tissues of the target animal dosed at the maximum use level requested.</p> <p><b>Total Residue Depletion Study</b></p> <p>The sponsor must demonstrate the depletion of total additive-related residue in edible tissues of target animals at times after the last administration of the compound. For large animals, the edible tissues are muscle, liver, kidney, fat, and, where appropriate, milk. For poultry, the edible tissues are muscle, liver, skin with adhering fat, and, where appropriate, eggs.</p>	<p>Mammalian toxicological data and pertinent livestock toxicity data are referenced for both target animal and human safety</p> <p><b>Rate and Degree of Absorption Distribution, Metabolism and Elimination Data:</b></p> <ul style="list-style-type: none"> <li>-- Acute Toxicity</li> <li>-- Acute Median Lethality</li> <li>-- Skin/Eye Irritation</li> <li>-- Skin Sensitization</li> <li>-- -Mutagenicity</li> <li>-- Short-Term Toxicity</li> <li>--Teratogenicity</li> <li>-- Developmental Toxicity</li> <li>-- Reproductive Toxicity</li> <li>-- Carcinogenicity</li> <li>-- Epidemiological Studies</li> <li>-- Chemical Interaction</li> </ul> <p>In particular for food safety, the following studies are required in the event that a residue may be present in the food produced -- i.e., meat, milk, eggs, fish.</p> <p>-- Suggested Maximum Residue Limit (MRL)</p>	<p><b>Metabolic and residue studies</b></p> <p>The establishment of the metabolic fate of the additive in the target species is a determinant step in the identification and quantification of the residues in the edible tissues or products. Studies must be submitted concerning the absorption, distribution, metabolism and excretion of the substance (and its metabolites).</p> <p><b>Metabolic Studies</b></p> <p>Metabolic balance following a single-dose administration of the active substance at the doses proposed for use (total amount corresponding to the daily intake) and possibly a multiple dose (if justified) to assess an approximate rate and extent of the absorption, distribution (plasma/blood) and excretion (urine, bile, feces, milk or eggs, expired air, excretion via gills) .</p> <p>Metabolic profiling, identification of the metabolite(s) in excreta and tissues and distribution in tissues and products shall be established following repeated dose administration of the labeled compound to animals to the steady state (metabolic equilibrium) identified by plasma levels.</p>

TABLE 2: Information required in the safety assessment/risk assessment processes (continued)

Concern	USA <sup>1</sup> (food additive)	CANADA <sup>2</sup> (feed ingredient)	EU <sup>3</sup> (feed additives)
	<p><b>Metabolism Studies In Laboratory Animals</b>                      Studies to determine whether the metabolites that people will consume from tissues of target animals are also produced by metabolism in the laboratory animals used for the toxicological testing. The studies should include compounds being tested for carcinogenicity and other toxicological endpoints.</p> <p>Repeat-dose toxicity testing (VICH GL31 and VICH GL37)                      Reproduction toxicity testing (VICH GL22)                      Developmental toxicity testing (VICH GL32)                      Genotoxicity testing (VICH GL23)                      Testing for effects on the human intestinal flora (VICH GL36) (FDA GFI 3; GFI 33)</p> <p>May require a set tolerance (FAPs and NADAs) (21 CFR 571.1 and 21 CFR 514).</p>	<p>or Tolerance                      -- Livestock Metabolic Fate And Residue Studies                      -- Metabolic Fate and Elimination Studies                      -- Residue Studies for the Parent Compound and its Possible Metabolites (current guidance T-3-141 s2; to be included as RG1, Chapter 2.5)</p> <p>Should it be determined that the use for the ingredient may result in residues, CFIA will consult with Health Canada for support of the Safety Determination.</p> <p>Data requirements as listed in RG -1, Ch. 2.3, 2.4, 2.5, 2.6, and/or 2.7 (depending on the nature of the ingredient).</p>	<p><b>Residue Studies</b> are required when residues are not a significant natural constituent of the body or fluids                      -- For major species, studies shall simultaneously evaluate the total residues of toxicological significance and identify the marker residue of the active substance in edible tissue (liver, kidney, muscle, skin, skin plus fat) and products (milk, eggs and honey).                      -- Withdrawal studies are described by animal number in the guidance                      -- Metabolic and disposition studies                      -- Bioavailability of residues</p> <p><b>Toxicological studies</b>                      (1) Acute toxicity                      (2) Genotoxicity (mutagenicity, clastogenicity)                      (3) Sub-chronic oral toxicity                      (4) Chronic oral toxicity/carcinogenicity                      (5) Reproduction toxicity including teratogenicity                      (6) Other studies.</p> <p>A toxicological NOAEL must be established                      -- Proposal of an acceptable daily intake (ADI) for the active substance. For micronutrients such as minerals and vitamins, it is usually more appropriate to use the concept of ULs (Tolerable Upper -intake Level) rather than ADIs                      --Calculation of consumer exposure.                      --Comparison of the ADI or the UL with consumer exposure considering all possible sources of the additive.                      (EC) No 429/2008</p> <p><b>Transfer of resistance to antimicrobials and shedding of enteropathogens</b>                      Studies shall be provided to determine the ability of the additive to induce cross-resistance to antibiotics used in human or veterinary medicine, to select resistant bacterial strains under field conditions in target species, to give rise to effects on opportunistic pathogens present in the digestive tract, to cause shedding or to</p>

TABLE 2: Information required in the safety assessment/risk assessment processes (continued)

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Concern	USA <sup>1</sup> (food additive)	CANADA <sup>2</sup> (feed ingredient)	EU <sup>3</sup> (feed additives)
<b>Worker Safety</b>	If warranted, FDA may require information on the label regarding worker safety issues, as specified in MSDS, in support of food additives . Generally data is required only in new animal drug applications	<p><b>Human Exposure Data And Exposure Estimation</b></p> <p>a) Major routes of exposure                      b) Amount of product handled by workers and consumers                      c) Frequency and duration of exposure                      d) Exposure concentrations                      e) Exposure studies                      (Data requirements as listed in RG-1, Ch. 2.3, 2.4, 2.5, 2.6, and/or 2.7 (depending on the nature of the ingredient)                      MSDS required                      Labeling requirements when needed</p>	<p>excrete zoonotic micro-organisms. (EC) No 429/2008</p> <p><b>Toxicological risk assessment for user/worker safety</b> (inhalation, dermal, mucosal, allergenicity, optic, and toxicity (from consumer safety data).                      -- Exposure assessment                      -- Mitigating measures (EC) No 429/2008                      MSDS required                      Labeling requirements when needed                      Specific labeling requirements for Microorganisms&gt;Biosafety 1</p>
<b>Environmental Safety</b>	Only to be addressed in Food Additive Petitions, not required for AAFCO definition process or GRAS notifications. Either the requirement for a full environmental assessment can be waived under specific categorical exclusions (21 CFR 25.30, 25.32, or 25.33) or if no exclusion, an environmental assessment must be provided in the submission that covers the use and disposal of the ingredient. The EA is a public document for which FDA requests public input. FDA must issue in response to the filing of either a Finding Of No Significant Impact (FONSI) or an Environmental Impact Statement. (21 CFR 25.40, 25.41, and 25.42).	<p><b>Feed may not be introduced that:</b></p> <p>a) Has or that may have an immediate or long-term harmful effect on the environment.                      (b) Constitutes or that may constitute a danger to the environment on which human or animal life depends.                      (c) Constitutes or that may constitute a danger in Canada to human or animal life or health. (Feed Regs, Sec. 2(2).)</p> <p><b>Determination of Environmental Fate And Effects (Studies required)</b></p> <p>-- Vapor Pressure and Volatilization                      -- Hydrolysis                      -- Photodegradation                      -- Adsorption-Desorption                      -- Biotransformation in Soil                      -- Biotransformation in aquatic systems                      -- Biochemical oxygen demand                      -- Toxicity to aquatic organisms                      -- Toxicity to soil organisms                      -- Toxicity to birds                      -- Toxicity to wildlife                      (Data requirements as listed in RG-1, Ch. 2.3, 2.4, 2.5, 2.6, and/or 2.7 (depending on the nature of the ingredient)</p>	<p>To determine if the additive or its metabolites may be excreted and exert an adverse impact on the environment an approach based in different steps is used.                      Predicted Environmental Concentration (PEC) may be required to be calculated.                      Phase I serves to identify those additives that do not need further testing (natural or physiological substance with no increase in the environment, substance intended for nonfood-producing animals, or when the PEC is very low). For the other situations a second phase (Phase II) assessment is needed to provide additional information, based upon which further studies may be considered necessary. (Directive 67/548/EEC)                      Phase II: Phase II is to assess the potential for additives to affect non-target species in the environment, including both aquatic and terrestrial species or to reach groundwater at unacceptable levels. The Phase II assessment is based on a risk quotient approach, where the calculated PEC and Predicted No Effect Concentration (PNEC) values for each compartment shall be compared. A PEC/PNEC &gt;1 requires a full environmental risk assessment.</p>

TABLE 2: Information required in the safety assessment/risk assessment processes (continued)

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Concern	USA <sup>1</sup> (food additive)	CANADA <sup>2</sup> (feed ingredient)	EU <sup>3</sup> (feed additives)
<b>Additives Effect on Livestock Product Evaluation</b>	Generally no requirement for meat, milk, or egg quality testing (may be required for certain food additives). Generally required for animal drugs.	Studies must be conducted to determine if significant changes in the chemical or physical composition of livestock products are produced when the feed is used (Feeds Regs)	(EC) No 429/2008  Meat, milk, egg, honey, quality studies may be required unless adequately justified to be not needed. (EC) No 429/2008
<b>Description of Additive</b>	IDENTITY OF THE ADDITIVE: -- Chemical identity -- Composition of the food additive, its physical, chemical, and biological properties, and specifications prescribing the minimum content of the desired component(s) and identifying and limiting the reaction byproducts and other impurities. (21 CFR 571.1)	-- Clear Identification of the ingredient -- Physicochemical Data --Composition of the ingredient --Consideration of contaminants Data requirements as listed in RG-1, Ch. 2.3, 2.4, 2.5, 2.6, and/or 2.7 (depending on the nature of the ingredient).	IDENTITY OF THE ADDITIVE -- Name of the additive -- Qualitative and quantitative composition (active substance/agent, other ) Physical state -- Purity -- Proposal for classification  Physical and chemical properties shall be given. Dissociation constant, pKa, electrostatic properties, melting point, boiling point, density, vapor pressure, solubility in water and in organic solvents, Kow and Kd/Koc, mass spectrometry and absorption spectra, NMR data, possible isomers and any other appropriate physical properties shall be provided, where appropriate. (EC) No 429/2008  Specific requirements for chemical substances; mixtures in which the constituents cannot be described by a single chemical formula; enzyme and enzyme preparations; substance produced via fermentation, micro-organisms are described in (EC) No 429/2008  For GMOs the description of the genetic modifications shall be given. The unique identifier for each GMO, as referred in Commission Regulation (EC) No 65/2004 of 14 January 2004 establishing a system for the development and assignment of unique identifiers for genetically modified organisms, shall be included.

TABLE 2: Information required in the safety assessment/risk assessment processes (continued)

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Concern	USA <sup>1</sup> (food additive)	CANADA <sup>2</sup> (feed ingredient)	EU <sup>3</sup> (feed additives)
<b>Utility/ Efficacy</b>	<p>Data establishing that the food additive will have the intended physical or other technical effect or that it may reasonably be expected to become a component, or to affect the characteristics, directly or indirectly, of food and the amount necessary to accomplish this. These data should include information in sufficient detail to permit evaluation with control data. (21 CFR 571.1)</p> <p>To address this requirement, FDA requires sufficient well-designed and carried out scientific studies to support that the additive can be expected to serve its intended use under various feed and animal systems in the US. Ingredients subject to food additive petitions generally require at least 3 scientifically sound, geographically distinct, and statistically analyzed studies for each major species.</p>	<p>Data to demonstrate the “conditions and the prevalence of such conditions under which the feed would be efficacious for its intended purposes” (Feeds Regs). Specific requirements depend on the intended purpose of the new ingredient, but typically a minimum of 3 scientific studies in support of a nutritional purpose carried out by qualified research personnel, using suitable methods, designed to facilitate statistical analysis, analyzed by appropriate statistical methods, and conducted under conditions similar to those that may be expected to occur in Canada. Certificates of analysis and analytical methodology substantiating the guarantee in the ingredient as well as in a mixed feed matrix may be required. (RG-1, chapter 2.3; for some product types, see Chapter 3.).</p>	<p>Based on studies intended to demonstrate the efficacy of an additive in terms of the aims of its intended use (category and function requested by the applicant) as defined in Article 6 (1) and Annex I of Regulation (EC) No 1831/2003. (EC) No 429/2008.</p> <p><b>In vitro studies</b> are usually sufficient for all technological and some sensory additives affecting the characteristics of feed.</p> <p><b>Short-term efficacy studies</b> e.g. bioavailability studies, digestion/balance studies, or other as justified</p> <p><b>Long-term efficacy studies</b> (two different locations). Duration is specified in guidance (annex IV)</p> <p><b>For zootechnical additives</b> at least two geographical locations are required, and generally long-term studies unless otherwise justified.</p> <p><b>Coccidiostats and histomonostats:</b> specific effects of the additive (e.g. species controlled) and its prophylactic properties (e.g. reduction in morbidity, mortality, oocyst count and lesion score). Information on the effect on growth and feed conversion (fattening birds, replacement layers and rabbits), effects on hatchability (breeding birds) shall be provided, as appropriate.</p> <p>(EC) No 429/2008</p>

TABLE 2: Information required in the safety assessment/risk assessment processes (continued)

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Concern	USA <sup>1</sup> (food additive)	CANADA <sup>2</sup> (feed ingredient)	EU <sup>3</sup> (feed additives)
Manufacturing	<p>The petition shall supply a list of all substances used in the synthesis, extraction, or other method of preparation, regardless of whether they undergo chemical change in the process. Each substance should be identified by its common English name and complete chemical name, using structural formulas when necessary for specific identification. If any proprietary preparation is used as a component, the proprietary name should be followed by a complete quantitative statement of composition. Reasonable alternatives for any listed substance may be specified. (21 CFR 571.1)</p> <p>In addition FDA requires a full understanding of each control point in the manufacture and specifications for all ingredients (AAFCO PPT, Manufacturing chemistry). For a NADA, changes in manufacturing process must be reported to FDA; this is not a requirement for food additives. (21 CFR 514)</p>	<p>A general description of the production and formulation processes, identifying raw materials, chemical reactions, techniques, and any other parameters which may influence the specifications, quality, or safety of a product. A flow-chart diagram accompanying the description is recommended. (See the appropriate RG, 1-chapters for more specifics -- depends on ingredient type)</p>	<p>To identify the critical points of the process that may have an influence on the safety of the additive, a description of the manufacturing process shall be given.</p> <p>A listing of all raw materials used in the manufacture of the ingredient as well as the accompanying MSDS is required. Reg (EC) No 429/2008</p>
Specifications	<p>Specific to the substance, based on compositional testing and what is known regarding the additive</p>	<p>The exact formulation of a particular product may vary, depending upon the manufacturer. A precise description of ingredients, including contaminants, is needed to properly assess product safety. Examples of acceptable analytical methods for contaminant detection include nuclear magnetic resonance (NMR) spectrums or gas chromatography (GC) profiles. (See the appropriate RG, 1-chapters for more specifics -- depends on ingredient type)</p>	<p>Applicant submits a proposal for specification. Concerns as based on type of substance, these may include:</p> <ul style="list-style-type: none"> <li>-- For micro-organisms: microbiological contamination, mycotoxins, heavy metals.</li> <li>-- For fermentation products (not containing micro-organisms as active agents): They shall follow the same requirements as for micro-organism products (see above). The extent to which spent growth medium is incorporated into the final product shall also be indicated.</li> <li>-- For plant-derived substances: microbiological and botanical contamination (e.g. castor oil plant, weed seeds, rye ergot in particular), mycotoxins, pesticide contamination, maximum values for solvents and, where appropriate, substances of toxicological concern known to occur in the original plant.</li> <li>-- For animal-derived substances:</li> </ul>

TABLE 2: Information required in the safety assessment/risk assessment processes (continued)

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Concern	USA <sup>1</sup> (food additive)	CANADA <sup>2</sup> (feed ingredient)	EU <sup>3</sup> (feed additives)
			<p>microbiological contamination, heavy metals and maximum values for solvents, where appropriate.</p> <p>-- For mineral substances: heavy metals, dioxins and PCBs.</p> <p>-- For products produced by chemical synthesis and processes: all chemicals used in the synthetic processes and any intermediate products remaining in the final product shall be identified and their concentrations given. The selection of mycotoxins for analysis shall be made according to the different matrices, where appropriate. (EC) No 429/2008</p>
<p>Analytical Methods</p>	<p>-- Validated method of analysis for the substance</p> <p>-- Validated methods of analysis for determination of substance in the complete feed</p> <p>-- Validated methods of analysis for residues in milk, meat or eggs required only for assessment of residue potential.</p>	<p>An acceptable test method for the analysis of the product must be provided. (T-3-141)</p> <p>Suitable methodology needed for the detection of significant amounts of any ingredient, compound, substance or organism that is intentionally incorporated into the feed or that occurs as a contaminant of the feed.(Feeds Regs)</p> <p>Certificates of analysis required in support of the label guarantee using the proposed methodology</p> <p>Also for safety, may require analytical methods for inherent contaminants or ingredient in final feed (RG-1, chapter 2.4 and 2.5)</p>	<p>The analytical methods to be used should be for the purpose of the official control of the additive as such, in premixtures, and in feedingstuffs shall be described.</p> <p>The methods submitted should be either:</p> <p>-- The ones in relevant Community rules where they exist; or the ones in internationally recognized rules or protocols.</p> <p>-- Are fit for the intended purpose, developed in accordance with scientific protocols and validated in a ring test in accordance with an internationally recognized protocol on collaborative trials (e.g. ISO 5725 or IUPAC).</p> <p>-- Are validated in-house according to international harmonized guidelines.</p> <p>In the case of additives resulting in residues on food of animal origin, the method(s) to be used for the analysis for the official controls of its metabolites in food of animal origin shall be included.</p> <p>-- Validated methods of analysis for the active substance for use in the product, premix and the feed.</p> <p>-- When an MRL is required a validated methods of analysis for residues of the additive or of its metabolites in food.</p> <p>In the case of coccidiostats and histomonostats which are also authorized as veterinary drugs the</p>

TABLE 2: Information required in the safety assessment/risk assessment processes (continued)

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Concern	USA <sup>1</sup> (food additive)	CANADA <sup>2</sup> (feed ingredient)	EU <sup>3</sup> (feed additives)
			<p>MRLs and the methods of analysis are the same ones reviewed by EMEA.</p> <p>-- Validated methods of the analysis relating to the identity and characterization of the additive, when required (EC) No 429/2008</p> <p>Methods must follow the format of ISO 78-2</p>
Stability	<p>-- Stability of the additive in the intended marketed container</p> <p>-- Stability of the additive once mixed into feed (AAFCO PPT, Manufacturing Chemistry)</p>	<p>This is the length of time the product can be stored without alterations to its chemical or biological integrity. This includes storage times under ideal conditions, a description of the factors affecting shelf life, what happens when the product degrades or decays, how one can tell if degradation has occurred, whether this creates a particular hazard, and how the manufacturer has substantiated its estimation of shelf life. Shelf-life should be determined based upon sensory/quality assessment, nutrient loss profiles, and perishability time. (See the appropriate RG, 1-chapters for more specifics -- depends on ingredient type)</p>	<p>The stability of each formulation of the additive, on exposure to different environmental conditions (light, temperature, pH, moisture, oxygen and packing material) shall be studied. Expected shelf-life of the additive as marketed should be based on at least two model situations covering the likely range of use conditions (e.g., 25 oC, 60% relative air humidity (HR) and 40 oC, 75% HR). (EC) No 429/2008</p>
Homogeneity in Feeds	<p>Required testing batches of feed to demonstrate the mixability of the additive in feed (AAFCO, PPT-Manufacturing Chemistry; 21 CFR 514.1 (b)(5))</p>	<p>Not typical, but depends on the ingredient (personal communication, CFIA). Also feeds intended to provide nutrition above normally (Table 4) (Feed Regs Section 5).</p>	<p>The capacity for homogeneous distribution of the feed additive (other than flavoring compounds) in premixtures, feedingstuffs or water must be demonstrated. (EC) No 429/2008</p>
Post-Marketing Plans	<p>None are required for food additives, required for approved animal drugs (21 CFR 514.80)</p>	<p>Not generally required for typical feed ingredients; however, needed for some specialty feeds such as diluted drug premixes (personal communication, CFIA).</p>	<p>In the case of substances that are recognized antibiotics and its use shown to select resistant bacterial strains, field studies to monitor for bacterial resistance to the additive have to be undertaken as part of postmarket monitoring.</p> <p>For coccidiostats and histomonostats, field monitoring of Eimeria spp. and Histomonas meleagridis resistance have to be undertaken (EC) No 429/2008</p> <p>Marketing of products consisting of, containing or produced from GMOs also must include a proposal for post-market monitoring. (EC) 1830/2003</p>

TABLE 2: Information required in the safety assessment/risk assessment processes (continued)

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<b>Concern</b>	<b>USA<sup>1</sup> (food additive)</b>	<b>CANADA<sup>2</sup> (feed ingredient)</b>	<b>EU<sup>3</sup> (feed additives)</b>
<b>Samples to be provided</b>	None for food additives.	Typically, requests sample for a new ingredient	3 samples (EC) No 429/2008. In addition applicant shall maintain reference samples valid for the entire period of the authorization of the feed additive by supplying new reference samples to the CRL to replace those expired.
<b>Withdrawal Periods</b>	The feed additives may require restrictions for use based on physiological status or age of animal, do not generally provide a withdrawal period. Withdrawal periods are used for pharmaceutical products, approved under a New Animal Drug Application, as listed in 21 CFR 558	The feed ingredient registration may provide restrictions for use based on physiological status or age of animal, does not generally provide a withdrawal period. (personal communication/CFIA)	Proposal of withdrawal period and Maximum Residue Levels must be provided by the applicant where appropriate. (EC) No 429/2008
<b>Proprietary</b>	All food additive are non-proprietary.	CFIA makes a determination based in part on safety and efficacy considerations, whether approved ingredients will be listed in part 1 or part 2 of schedules IV and V; ingredients listed in part 1 are exempt from registration as long as they meet the composition and labeling requirements of the Feeds Regulations, and those listed in part 2 require registration of each source prior to import or sale due to safety or efficacy concerns with the source of that ingredient. Therefore registered part 2 ingredients may be considered proprietary. (personal communication/CFIA)	All technological, sensory and nutritional additives have nonholder-specific authorizations.  Authorizations for zootechnical additives, for coccidiostats, histomonostats, as well as for additives consisting, containing or produced from GMOs are “holder-specific authorizations” (proprietary).
<b>Approval Period</b>	Until the regulation/non-objection is found to be invalid or unsafe and FDA removes it.	Registered mixed feeds and part 2 single ingredient feeds must be re-registered every 3 years. Single Feed Ingredients in part 1 (schedules IV and V) are permanent unless CFIA finds the listing invalid or unsafe.	Ten years of authorization, with renewal after the 10 years on the basis of specific application.

<sup>1</sup> The outlined US requirements cover the general requirements for substances that must be approved for use through a Food Additive Petition (FAP), which are similar and breadth for a New Animal Drug Application (NADA). FDA relies on a number of the animal drug guidance for the safety evaluation of feed ingredients. FDA also has an MOU with AAFCO in which FDA must issue a letter of concurrence regarding the suitability of the feed ingredient for its proposed use from FDA prior to adopting new feed ingredient definitions or amending existing ones. The FDA provides this scientific review through an informal procedure. This procedure is only used when there are no significant safety concerns for the product; as such the safety submission does not always conform to what is provided in the table above; also FDA does not generally require a full battery of utility studies to support these definitions (AAFCO PPT: Feed Ingredient Utility). Also in the newly adopted voluntary GRAS notifications that are based on published literature, these outlined requirements will not

TABLE 2: Information required in the safety assessment/risk assessment processes (continued)

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be strictly followed (75 FR 31800). Plant-based material for genetically altered plants has its own specific process not described in this table (May 29, 1992 FR). Color additives for animal feed use are evaluated by the Center for Food Safety and Applied Nutrition, under the regulations 21 CFR 73, and submission requirements do not follow the outline provided above.

<sup>2</sup>The outlined Canadian requirements cover the requirements for unapproved single-feed ingredients, as regulated by the Canadian Food Inspections Agency (Feed Regulations). The New Drug Submissions approval requirements are found in Part C, Division 8 of the Food and Drug Regulations.

<sup>3</sup> The outlined European requirements are specific to feed additives as defined in Regulation 429/2008. These requirements are not required for processing aids and veterinary medicinal products (defined in Directive 2001/82/EC) as they are excluded from the scope of Regulation 1831/2003 on feed additives. Coccidiostats and histomonostats are included in the scope of Regulation (EC) No 1831/2003 on feed additives and have specific requirements under Regulation 429/2008. The evaluation process takes into account if the product is also authorized in food especially to address the human health part of the assessment and not the animal health or the environmental aspects. For micro-organisms, a system called QPS (Qualified Presumption of Safety) is also inducing reduced requirements in the evaluation by the European Food Safety Agency (EFSA) In addition to the requirements for feed additive applications in Regulation (EC) No 429/2008 there is additional guidance published by EFSA and by the CRL.

**TABLE 3. PERMITTED INTENDED USE OR FUNCTION<sup>1</sup> FOR FEED INGREDIENTS**

<b>Intended Use/Function</b>	<b>US (food additives)</b>	<b>Canada (feed)</b>	<b>EU<sup>2</sup>(feed additives)</b>
Nutrition	YES	YES	NO, Most are feed materials YES, some are category 3 Feed additives (eg. Vitamins and minerals)
Taste (flavor) or aroma	YES	YES	YES, Category 2 (sensory)
Additives that technically affect the feed (e.g. pellet binding agent, antioxidant, anticaking agent, flow agent, emulsifier, chelating agent, antifoaming agent etc)	YES	YES	Processing Aid <sup>3</sup> -- not regulated YES-Other Technical Additives (category 2)
Viable microorganisms	YES	YES	YES, Category 4 (Zootechnical)
Color feed	YES (color additive petition)	YES	YES, Category 2(sensory)
Color flesh	YES (color additive petition)	YES	YES, Category 2(sensory)
Additives that protect nutrients from rumen digestion	YES	YES	YES, Category 2 (technological additives), in some cases
Additives intended to favorably affect the environment	YES	YES	YES, Category 4 (Zootechnical)
Salmonella control	YES	NO (animal drug)	YES, Category 1 (Technological additives-preservative)
Modification of Intestinal Flora	YES, effect in feed NO, effect on animal (animal drug)	NO (animal drug)	YES, Category 4 (Zootechnical)
Improved/increased feed intake	YES	YES	YES, Category 4 (Zootechnical)
Increase production of animal product (meat, milk, eggs) -Increased milk fat % -Increased milk protein % -Improved feed conversion	NO (animal drug)	YES <sup>4</sup> (within “normal range”, for viable microorganisms and cell walls ) NO <sup>4</sup> -- for other foods, or increases “beyond normal range”	YES, Category 4 (Zootechnical)
Coccidiostatic	NO (animal drug)	NO (animal drug)	YES, Category 4 (Zootechnical), for prevention only
Histomonostatic	NO (animal drug)	NO (animal drug)	YES, Category 4 (Zootechnical), for

TABLE 3. PERMITTED FUNCTION<sup>1</sup> OR CLAIM FOR FEED INGREDIENTS (continued)

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Intended Use/Function	US (food additives)	Canada (feed)	EU <sup>2</sup> (feed additives)
			prevention only
Prevent, mitigate or treat disease, disorder, abnormal physical state, or its symptoms	NO (animal drug or vaccine)	NO (animal drug or vaccine)	YES -- Coccidiostats, for prevention only (category 5) YES-- Histomonostats , for prevention only (category 5) NO -- Other Disease (veterinary medicinal product)

<sup>1</sup>This table refers to functions ascribed to feed additives in the EU in which utility data is collected to support the authorization. See Appendix 2 for a full listing of function groups covered in Feed Additive categories .

<sup>2</sup>Herewith only the functions authorized for feed additives to be reflected in the labeling (on the compound feed to which the feed additive has been added) are mentioned. Claims of feeds, compound feeds, complementary feed, dietetic feed, are addressed by the Marketing of Feed Regulation (EC) No. 767/2009 and related legislation and not commented on here.

<sup>3</sup> EU defines “Processing aid” as a substance not consumed as a feedingstuff by itself, intentionally used in the processing of feedingstuffs or feed materials to fulfill a technological purpose during treatment or processing which may result in the unintentional but technologically unavoidable presence of residues of the substance or its derivatives in the final product, provided that these residues do not have an adverse effect on animal health, human health or the environment and do not have any technological effects on the finished feed.

<sup>4</sup> Canadian Regulatory Approach on Production Claims for Viable Microbial and yeast cell wall products (as stated in RG1, 3.22 & 3.23) are evaluated under the following; however, CFIA is willing to discuss these claims for other single feed ingredients

**Feed** -- Improvement of appetite, weight gain, feed efficiency and other production parameters to within normal ranges as defined in current National Research Council (NRC) or equivalent published literature, under normal conditions of animal husbandry. In the absence of NRC published values, the inclusion of a positive control group in an efficacy trial as a reference standard would be acceptable. Normal conditions of animal husbandry may include weaning, ration changes, vaccination, debeaking, dehorning, castration, shipping, etc.

**Drugs** -- Improvements of production parameters beyond normal (as defined in current NRC or equivalent published literature, under normal conditions of animal husbandry); treatment, mitigation (i.e. reduction in incidence and severity) or prevention of a disease, disorder, abnormal physical state, or its symptoms; any reference to intestinal flora; restoration, correction or modification of organic function; any stress-related claim will be evaluated on the basis of disease, disorder, abnormal physical state or their symptoms resulting from stressful conditions.

TABLE 4. IDENTIFICATION OF REGULATORY PROCESSES THROUGH TYPICAL NEW INGREDIENT EXAMPLES; WITH SPECIFIC REGULATORY GUIDANCE

FEED INGREDIENT/ FUNCTIONS	US	CANADA	EU
Enzyme	<b>Food additive</b> <sup>1</sup> : Label claim must be expressed as enzyme activity/time/wt. (AAFCO Enzyme PPT)	<b>Specialty product</b> (mixed feed): Safety considerations include standard safety (RG-1 section 2.4 and 2.7) as well as dermal/respiratory sensitization/irritation studies; required labeling (RG-1; section 3.6). Enzymes are not listed as ingredients in schedules IV/V, rather they are typically registered as a supplement with an enzyme activity guarantee (claim).	<b>Feed additive</b> ; Category 4; zootechnical
Enzymes obtained via GMO	<b>Food additive</b> : Label claim must be expressed as enzyme activity/time/wt. (AAFCO Enzyme PPT)	<b>Specialty product</b> (mixed feed) guidance is provided in RG1; section 2.7) available upon request Same as novel ingredients (RG1, section 2.4) <sup>2</sup>	Enzymes produced from a GMO (for example by fermentation with a genetically modified microorganism) have to follow the procedure of authorization of genetically modified food and feed in Regulation (EC) No 1829/2003 in addition to the authorization as a <b>Feed additive</b> under Regulation (EC) No.1831/2003
Nutraceuticals	Not an FDA-recognized classification of ingredients; generally regulated by intended use (see Table 3)	Not a CFIA regulatory term for animal feed; classification of ingredients generally regulated by claim/intended purpose	Not an EU regulatory term for animal feed; classification of ingredients generally regulated by function
Flavors-Natural (whole botanical)	<b>Food additive</b> : If listed as a human flavor (21 CFR 182 and 184) can be used without further review. (AFIA RTS, Alewynse PPT)	<b>Single ingredient feed</b> (RG1, section 3.8)	<b>Feed Material</b> : Whole plants, parts of plants or plants with limited processing can be marketed as feed materials (no preclearance requirements) and are not feed additives. Conversely, they cannot be listed as feed additives in the labeling.
Flavors-Natural	<b>Food additive</b> : If listed as a human flavor (21 CFR 182 and 184) can be used without further review. (AFIA RTS, Alewynse PPT)	<b>Single ingredient feed</b> (RG1, section 3.8)	<b>Feed additive</b> : Category 2, sensory additive
Flavor-Synthetics	<b>Food additive</b> (AFIA RTS, Alewynse PPT)	<b>Single ingredient feed</b> (RG1, section 3.8)	<b>Feed additive</b> Category 2, sensory additive

TABLE 4. IDENTIFICATION OF REGULATORY PROCESSES THROUGH TYPICAL INGREDIENT EXAMPLES; (continued)  
Page 2

FEED INGREDIENT/ FUNCTIONS	US	CANADA	EU
Color Additives for coloring the meat, tissues, eggs	<b>Color Additive Petition</b> (see 21 CFR 73)	<b>Single ingredient feed</b>	<b>Feed additive;</b> Category 2, sensory additive
Viable Microorganism	<b>Food additive</b> ; utility may be based on number of live microorganisms/weight (AFIA RTS, Alewynse PPT)	Depending on the extent of the claim they may be regulated as a feed or an animal drug: <b>Feed:</b> Improvement of appetite, weight gain, feed efficiency and other production parameters to within normal ranges as defined in current National Research Council (NRC) or equivalent published literature, under normal conditions of animal husbandry. In the absence of NRC published values, the inclusion of a positive control group in an efficacy trial as a reference standard would be acceptable. Normal conditions of animal husbandry may include weaning, ration changes, vaccination, debeaking, dehorning, castration, shipping, etc. <b>Animal Drug:</b> Improvements of production parameters beyond normal (as defined in current NRC or equivalent published literature, under normal conditions of animal husbandry); treatment, mitigation (i.e. reduction in incidence and severity) or prevention of a disease, disorder, abnormal physical state, or its symptoms; any reference to intestinal flora; restoration, correction or modification of organic function. Any stress-related claim will be evaluated on the basis of disease, disorder, abnormal physical state or their symptoms resulting from stressful conditions. (RG1; section 3.22)	<b>Feed additive:</b> zootechnical additives Most microorganisms authorized as feed additives under Regulation 1831/2003

TABLE 4. IDENTIFICATION OF REGULATORY PROCESSES THROUGH TYPICAL INGREDIENT EXAMPLES; (continued)

FEED INGREDIENT/ FUNCTIONS	US	CANADA	EU
		Novel feed guidelines apply -- safety and efficacy requirements are listed in RG1, Ch. 2.7, Novel Feed Guidelines (available upon request)	
Viable Yeast	<b>Food additive:</b> Utility may be based on number of live yeast/weight (AFIA RTS, Alewynse PPT)	<b>Single ingredient feed</b> (see above). Include standard safety as per RG1 section 2.4 and 2.7.	<b>Feed additive:</b> zootechnical additives. Most microorganisms authorized as feed additives under Regulation 1831/2003.
Yeast Cell Walls	<b>Food additive</b> (no specific guidance)	<b>Single ingredient feed</b> (see above). Include standard safety as per RG1 section 2.4 and 2.7 (RG1; section 3.23) may include some production claims (see viable microorganism)	Depending on Use: <b>Feed material</b> , if a source of nutrition <b>Feed additive</b> if a specific function
Vitamin, Amino Acid or Trace Mineral	<b>Food additive</b>	<b>Single ingredient feed</b>	<b>Feed Additive:</b> Category 3 nutritional additives
Macro Minerals	<b>Food additive</b>	<b>Single ingredient feed</b>	<b>Feed Material</b>
Non-Viable Microorganisms	<b>Food additive</b> (no specific guidance)	<b>Single ingredient feed:</b> Some are schedule IV, part 1 ingredients and do not require additional review. If not listed in schedule IV a full safety and efficacy review is required as per the Novel Feed Guidelines, RG1, ch. 2.7. Additional labeling statements may be required.	Depending on Use: <b>Feed material</b> , if a source of nutrition <b>Feed additive</b> if a specific function (for example source of selenium).
Probiotics/Prebiotics -- gut-flora stabilizer	Regulate as <b>feed</b> or <b>animal drug</b> , dependent on intended use. (Complementary and Alternative Medicine Guidance (CDER/FDA))	Regulated as a <b>veterinary drug</b> under the federal Food and Drugs Act by the Veterinary Drug Directorate; Health Canada	<b>Feed additive:</b> generally classified as a zootechnical additive (gut-flora stabilizer). EC 429/2008
Salmonella Control in Feed	<b>Food additive:</b> If effect is on the feed, specific guidance (GFI 80) to demonstrate utility <b>Animal Drug:</b> If effect is on the animal (see 21 CFR 514)	Regulated as <b>veterinary drugs</b> under the federal Food and Drugs Act by the Veterinary Drug Directorate; Health Canada	<b>Feed additive</b> Category 1- Technological Additive (preservative)
Mold Inhibitor on Feed	<b>Food additive</b> (no specific guidance)	<b>Single ingredient feed</b>	<b>Feed additive</b> Category 1- Technological Additive (preservative)
Plants altered through biotechnology (GMO Plants)	Premarket biotechnology notification (see 66FR4706)	Application for the authorization of the release of a novel feed. (See RG1;	<b>Feed Additives</b> have to follow the procedure of authorization of

TABLE 4. IDENTIFICATION OF REGULATORY PROCESSES THROUGH TYPICAL INGREDIENT EXAMPLES; (continued)

Page 4

FEED INGREDIENT/ FUNCTIONS	US	CANADA	EU
		section 2.6)	genetically modified food and feed in Regulation (EC) No 1829/2003 in addition to the authorization as a <b>Feed additive</b> under Regulation (EC) No.1831/2003
Additives Produced from a Genetically Modified Organism	<b>Food additive:</b> safety considerations include demonstration that genetic modification will not result in unintended safety hazard (no specific guidance)	<b>Single ingredient feed:</b> Guidance -- safety and efficacy requirements are listed in RG1, ch. 2.7, Novel Feed Guidelines (available upon request). Need to demonstrate safety and efficacy as per Novel Feed Guidelines <sup>2</sup>	<b>Feed Additives</b> have to follow the procedure of authorization of genetically modified food and feed in Regulation (EC) No 1829/2003 in addition to the authorization as a <b>Feed additive</b> under Regulation (EC) No.1831/2003
Processing Aid /Technological Additive	<b>Food additive:</b> Utility testing is in the feed; target animal safety studies may be waived (no specific guidance)	<b>Single ingredient feed:</b> Utility testing is in the feed; feed homogeneity testing sometimes required (RG1; e.g. sections 3.1, 3.2, 3.3, 3.16, and 3.17)	<b>Processing aids</b> are not regulated (see definition section) as feed additives. <b>Technological Additives</b> are feed additives, Category 1
Ingredients Specific for Companion Animals/Pets	<b>Food additive:</b> no human food safety requirements, extensive target animal safety requirements (no specific guidance)	Feed intended for companions animals are not regulated domestically in Canada. Some control under Health of Animals Act and Regulations, for imports and exports.	<b>Feed additive:</b> category dependent on function
Ingredients Specific for Horses	Horses considered nonfood animals (see companion animal entry)	<b>Single ingredient feed</b> (considered a food- producing animal)	<b>Feed additive:</b> category dependent on function
Ingredients Specific for Use In Aquaculture	<b>Food additive</b> (specific guidance available on utility, GFI 53)	<b>Single ingredient feed</b> (no specific guidance)	<b>Feed additive:</b> category dependent on function
Feed Additives with Production Claim (Function)	<b>Animal Drug:</b> All feed ingredients with production claims require the approval of a New Animal Drug Application (21 CFR 514)	<b>General Guidance:</b> Depending on the type of product and claim (intended use) they may be regulated as a <b>feed</b> or <b>veterinary drugs</b> . See Viable Microorganism entry, above. (Personal communication with CFIA staff)	<b>Feed additive</b> ;Category 4- Zootechnical:
Feed Additives That Favorably Affect the Environmental Consequence (e.g. Phytase)	<b>Food additive</b> (no specific guidance)	<b>Single ingredient feed</b> (no specific guidance)	<b>Feed additive</b> , Category 4 Zootechnical:
Coccidiostats	<b>Animal Drug</b> (21 CFR 514)	<b>Veterinary Drug</b> Regulated under	<b>Feed additive</b> Category 5

TABLE 4. IDENTIFICATION OF REGULATORY PROCESSES THROUGH TYPICAL INGREDIENT EXAMPLES; (continued)  
Page 5

FEED INGREDIENT/ FUNCTIONS	US	CANADA	EU
		the federal Food and Drugs Act by the Veterinary Drug Directorate, Health Canada	
Histomonostats	<b>Animal Drug</b> (21 CFR 514)	<b>Veterinary Drug</b> Regulated under the federal Food and Drugs Act by the Veterinary Drug Directorate, Health Canada	<b>Feed additive</b> Category 5

<sup>1</sup>For this table the term FOOD ADDITIVE is used in a general sense and covers all premarket submissions evaluated by FDA to permit the marketing of a new ingredient (see report page 5).

<sup>2</sup>The Canadian regulatory system for products of biotechnology is product- rather than process-based. As a result, Canada has adopted a very broad definition of biotechnology and focused regulations on novel traits or “new” organisms rather than “genetic engineering” itself.

TABLE 5. PROHIBITED SUBSTANCES IN ANIMAL FEED

	US	Canada	EU
General Statement	<p>Adulterated foods cannot be introduced into US commerce. (FFDCA 301).</p> <p>A food is adulterated if it contains poisonous, insanitary, or deleterious ingredients (including an unsafe food additive or unrecognized feed additive) (FFDCA 402).</p>	<p>No person shall manufacture, sell or import into Canada in contravention of the regulations any feed that may adversely affect animal or human health. (Feeds Act)</p> <p>Canada has a positive list of ingredients. All ingredients used must be listed in schedules IV/V of the Feed Regulations.</p>	<p>Feed shall not be placed on the market or fed to any food-producing animal if it is unsafe.</p> <p>Feed shall be deemed to be unsafe for its intended use if it is considered to:</p> <ul style="list-style-type: none"> <li>-- Have an adverse effect on human or animal health.</li> <li>-- Make the food derived from food-producing animals unsafe for human consumption. (Article 15, REGULATION (EC) No 178/2002)</li> </ul>
Specific Ingredients	<p>Substances Prohibited for Use in Animal feed 21 CFR 589 (List includes gentian violet, animal proteins (certain restrictions), and propylene glycol).</p>	<p>Deleterious Substances (sections 3 and 4 of the Act:</p> <ul style="list-style-type: none"> <li>-- Aldrin.</li> <li>-- Carbaryl.</li> <li>-- Carbathiin.</li> <li>-- D.D.T..</li> <li>-- Dieldrin.</li> <li>-- Heptachlor.</li> <li>-- Heptachlor epoxide.</li> <li>-- Lindane.</li> <li>-- Malathion.</li> <li>-- Mercury compounds.</li> <li>-- Methoxychlor</li> <li>-- Toxaphene. (Feed Reg)</li> </ul> <p>In addition prohibited use of:</p> <ul style="list-style-type: none"> <li>-- Pet food (RG-3)</li> <li>-- Poultry Manure (RG-2)</li> <li>-- Gentian Violet (RG-1 ch 7.3)</li> <li>-- Animal protein restrictions (BSE)</li> </ul> <p>Health of Animals regulations (section 162(1) and 160 )</p>	<p>COMMISSION Decision of March 1, 2004, adopting a list of materials whose circulation or use for animal nutrition purposes is prohibited (OJL 67 5.3.2004) (In the process of being integrated under Regulation 767/2009)</p> <p>Prevention, control and eradication of certain transmissible spongiform encephalopathies (EC No 999/2001)</p> <p>Restrictions on certain animal by-products for the feed of certain animals (Regulation 1069/2009)</p>

## APPENDIX 1: ACRONYMS and DEFINITIONS

### ACRONYMS:

**AAFCO:** Association of American Feed Control Officials, a private, non-profit association of United States' federal and state feed regulatory officials that develop standards and models recognized in state laws

**CFIA:** Canadian Food Inspection Agency

**CFR:** Code of Federal Regulations for the United States federal government

**CN:** Canadian federal government (CFIA and Health Canada)

**CODEX:** Codex Alimentarius Commission was created by FAO and WHO in 1963 to develop food standards, guidelines and related texts such as codes of practice under the Joint FAO/WHO Food Standards Program.

**EFSA:** European Food Safety Authority

**EU:** European Union, or in the context of this report the EC, European Commission, which makes recommendations to member countries

**FAO:** Food and Agriculture Organization, United Nations

**FAP:** Food Additive Petition (FDA-US)

**FDA:** Food and Drug Administration, US federal government

**FFDCA:** Federal Food Drug and Cosmetic Act, US Government law

**FR:** Federal Register of the United States Government, the daily publication of rules, notices and procedures

**GFI:** Guidance for Industry (FDA-US)

**GMO:** Genetically Modified Organism

**GRAS:** Generally Recognized As Safe

**MSDS:** Material Safety Data Sheet

**NADA:** New Animal Drug Application (FDA-US)

**NOAEL:** No Observed Adverse Effect Level

**PBN:** Premarket Biotechnology Notice (FDA-US)

**PPM:** Policy and Procedure Manual (FDA-US)

**RG1:** Regulatory Guidance 1 (CFIA-CN)

**US:** United States federal government (Food and Drug Administration)

**VICH:** International Conference on Harmonisation of Technical Requirements for the Registration of Veterinary Products (EU-USA-Japan)

**WHO:** World Health Organization

### DEFINITIONS:

#### REGULATORY/LEGAL DEFINITIONS FOOD/FEED/FEED ADDITIVE

**EU Food (foodstuff):** Any substance or product, whether processed, partially processed or unprocessed, intended to be, or reasonably expected to be ingested by humans. (EU REGULATION (EC) No 178/2002, article 2)

**EU Feed (feedingstuff):** Any substance or product, including additives, whether processed, partially processed or unprocessed, intended to be used for oral feeding to animals. (EU REGULATION (EC) No 178/2002, article 2)

**EU Feed additives:** Substances, micro-organisms or preparations, other than feed material and premixtures, which are intentionally added to feed or water in order to perform, in particular, one or more of the functions mentioned in Article 5(3). (EC) No 1831/2003, article 2

**EU Feed materials:** Products of vegetable or animal origin, whose principal purpose is to meet animals' nutritional needs, in their natural state, fresh or preserved, and products derived from the industrial processing thereof, and organic or inorganic substances, whether or not containing feed additives, which are intended for use in oral animal-feeding either directly as such, or after processing, or in the preparation of compound feed, or as carrier of premixtures. REGULATION (EC) No 767/2009, Article 2

**EU: Feed Additive Categories** ((EC) No 1831/2003, article 6)

- (1) Technological additives
- (2) Sensory additives
- (3) Nutritional additives
- (4) Zootechnical additives
- (5) Coccidiostats and histomonostats

**CN Feed:** Any substance or mixture of substances containing amino acids, anti-oxidants, carbohydrates, condiments, enzymes, fats, minerals, non-protein nitrogen products, proteins or vitamins, or pelletizing, coloring, foaming or flavoring agents and any other substance manufactured, sold or represented for use:

- (a) for consumption by livestock,
  - (b) for providing the nutritional requirements of livestock, or
  - (c) for the purpose of preventing or correcting nutritional disorders of livestock;
- or any substance for use in any such substance or mixture of substances (Feeds Act)

**CN Novel feed:** A feed, comprising an organism or organisms, or parts or products thereof, that

- (a) is not set out in Schedule IV or V, or
- (b) has a novel trait. (Feed Regs)

**CN Novel trait:** A characteristic of the feed that:

- (a) has been intentionally selected, created or introduced into the feed through a specific genetic change, and
- (b) based on valid scientific rationale, is not substantially equivalent, in terms of its specific use and safety both for the environment and for human and animal health, to any characteristic of a similar feed that is set out in Schedule IV or V. (Feed Regs)

**US Food:** (1) Articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article. (FFDCA, 201(f))

**US Animal feed:** An article intended for use for food for animals other than man and that is intended for use as a substantial source of nutrients in the diet of the animal and is not limited to a mixture intended to be the sole ration of the animal. (FFDCA, 201 (w))

**US Food additive:** Any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use), if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use; except that such term does not include:

- (1) a pesticide chemical residue in or on a raw agricultural commodity or processed food; or
- (2) a pesticide chemical; or
- (3) a color additive; or
- (4) any substance used in accordance with a sanction or approval granted prior to the enactment of this paragraph pursuant to this Act [enacted Sept. 6, 1958], the Poultry Products Inspection Act (21 U.S.C. 451 and the following) or the Meat Inspection Act of March 4, 1907 (34 Stat. 1260), as amended and extended (21 U.S.C. 71 and the following);
- (5) a new animal drug; or
- (6) an ingredient described in paragraph (ff) in, or intended for use in, a dietary supplement. (FFDCA, 201(s))

**CODEX Feed (Feedingstuff):** Any single or multiple materials, whether processed, semi-processed or raw, which is intended to be fed directly to food producing animals.

**CODEX Feed Additive:** Any intentionally added ingredient not normally consumed as feed by itself, whether or not it has nutritional value, which affects the characteristics of feed or animal products.

**CODEX Feed Ingredient:** A component part or constituent of any combination or mixture making up a feed, whether or not it has a nutritional value in the animal's diet, including feed additives. Ingredients are of plant, animal or aquatic origin, or other organic or inorganic substances.

**CODEX Medicated Feed:** Any feed that contains veterinary drugs as defined in the Codex Alimentarius Commission Procedural Manual.

**CODEX Undesirable Substances:** Contaminants and other substances that are present in and/or on feed and feed ingredients and that constitute a risk to consumers' health, including food safety-related animal health issues.

## **OTHER REGULATORY/LEGAL DEFINITIONS**

**EU Food-producing animal:** Any animal that is fed, bred or kept for the production of food for human consumption, including animals that are not used for human consumption, but that belong to a species that is normally used for human consumption in the Community. ((EC) No 767/2009, Article 2)

**EU Genetically modified food:** Food containing, consisting of or produced from GMOs. (EC) No 1829/2003

**EU Genetically modified organism:** An organism, with the exception of humans, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination. Directive 2001/18/EC; (EC) No 1829/2003

**EU Hazard:** A biological, chemical or physical agent in, or condition of, food or feed with the potential to cause an adverse health effect. (EU REGULATION (EC) No 178/2002, article 3)

**EU Risk:** A function of the probability of an adverse health effect and the severity of that effect, consequential to a hazard. (EU REGULATION (EC) No 178/2002, article 3)

**EU Minor species:** Food-producing animals other than bovines (dairy and meat animals, including calves), sheep (meat animals), pigs, chickens (including laying hens), turkeys and fish belonging to the Salmonidae. (EC) No 429/2008

**EU non-food producing animals** means any animal that is fed, bred or kept ,not used for human consumption, such as fur animals, pets and animals kept in laboratories, zoos or circuses (Regulation 767/2009)

**EU Pet or Pet animal** means any non-food producing animal belonging to species fed, bred or kept, but not normally used for human consumption in the Community; (Regulation 767/2009)

**EU Precautionary principle:** In specific circumstances where, following an assessment of available information, the possibility of harmful effects on health is identified but scientific uncertainty persists, provisional risk management measures necessary to ensure the high level of health protection chosen in the Community may be adopted, pending further scientific information for a more comprehensive risk assessment. (EU REGULATION (EC) No 178/2002, article 7)

**EU Processing aids:** Any substance not consumed as a feedingstuff by itself, intentionally used in the processing of feedingstuff or feed materials to fulfill a technological purpose during treatment or processing which may result in the unintentional but technologically unavoidable presence of residues of the substance or its derivatives in the final product, provided that these residues do not have an adverse effect on animal health, human health or the environment and do not have any technological effects on the finished feed. Directive 2001/82/EC940

**EU Risk analysis:** A process of three interconnected components: risk assessment, risk management and risk communication. (EU REGULATION (EC) No 178/2002, article 3)

**EU Risk assessment:** A scientifically based process of four steps: hazard identification, hazard characterization, exposure assessment and risk characterization. (EU REGULATION (EC) No 178/2002, article 3)

**EU Risk management:** The process, distinct from risk assessment, of weighing policy alternatives in consultation with interested parties, considering risk assessment and other legitimate factors, and, if need be, selecting appropriate prevention and control options. (EU REGULATION (EC) No 178/2002, article 3)

**CN Livestock:** Horses, cattle, sheep, goats, swine, foxes, fish, mink, rabbits and poultry; includes such other creatures as may be designated by regulation as livestock for the purposes of this Act. (Feeds Act)

**US Bioengineered food:** Food derived from a plant that is developed using a transformation event. 66FR 4706

**US Drug** means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C). A food or dietary supplement for which a claim, subject to sections 403(r)(1)(B) and 403(r)(3) or sections 403(r)(1)(B) and 403(r)(5)(D), is made in accordance with the requirements of section 403(r) is not a drug solely because the label or the labeling contains such a claim. A food, dietary ingredient, or dietary supplement for which a truthful and not misleading statement is made in accordance with section 403(r)(6) is not a drug under clause (C) solely because the label or the labeling contains such a statement. (FFDCA 201(g)(1))

**US Generally Recognized As Safe:** May be based only on the views of experts qualified by scientific training and experience to evaluate the safety of substances directly or indirectly added to food. The basis of such views may be either (1) scientific procedures or (2) in the case of a substance used in food prior to January 1, 1958, through experience based on common use in food. General recognition of safety requires common knowledge about the substance throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food. (21 CFR 570.30(a))

**US Major species:** Cattle, horses, swine, chickens, turkeys, dogs, and cats, except that the secretary may add species to this definition by regulation. FFDCA

**US Minor species** are all animals other than humans that are not one of the major species. (MUMS Act, 2004)

**US Minor use** means the intended use of a drug in a major species for an indication that occurs infrequently and in only a small number of animals or in limited geographical areas and in only a small number of animals annually (MUMS Act, 2004)

**US New Animal Drug Application:** In this report it is defined specific to pharmaceutical agents and animal production drugs incorporated in animal feed (Medicated Feed). (21 CFR 514)

**US Premarket biotechnology notice:** A submission to FDA regarding a bioengineered food that is intended to enter commercial distribution. Under this part, a PBN includes all data and information in the original submission and in any amendments to the original submission. 66FR 4706

**US Transformation event:** The introduction into an organism of genetic material that has been manipulated in vitro. For the purpose of this part, “organism” refers to plants. 66FR 4706

## **Appendix 2 --FEED ADDITIVE CATEGORIES REGULATION (EC) No 1831/2003, ANNEX I**

### **1. In the category “technological additives,” the following functional groups are included:**

- (a) Preservatives: substances or, when applicable, microorganisms that protect feed against deterioration caused by microorganisms or their metabolites.
- (b) Antioxidants: substances prolonging the storage life of feedingstuffs and feed materials by protecting them against deterioration caused by oxidation.
- (c) Emulsifiers: substances that make it possible to form or maintain a homogeneous mixture of two or more immiscible phases in feedingstuffs.
- (d) Stabilizers: substances that make it possible to maintain the physicochemical state of feedingstuffs.
- (e) Thickeners: substances that increase the viscosity of feedingstuffs.
- (f) Gelling agents: substances that give a feedingstuff texture through the formation of a gel.
- (g) Binders: substances that increase the tendency of particles of feedingstuffs to adhere.
- (h) Substances for control of radionuclide contamination: substances that suppress absorption of radionuclides or promote their excretion.
- (i) Anticaking agents: substances that reduce the tendency of individual particles of a feedingstuff to adhere.
- (j) Acidity regulators: substances that adjust the pH of feedingstuffs.
- (k) Silage additives: substances, including enzymes or microorganisms, intended to be incorporated into feed to improve the production of silage.
- (l) Denaturants: substances which, when used for the manufacture of processed feedingstuffs, allow the identification of the origin of specific food or feed materials.
- (m) Substances for reduction of the contamination of feed by mycotoxins: substances that can suppress or reduce the absorption, promote the excretion of mycotoxins or modify their mode of action.

### **2. In the category “sensory additives,” the following functional groups are included:**

- (a) Colorants:
  - (i) substances that add or restore color in feedingstuffs.
  - (ii) substances that, when fed to animals, add colors to food of animal origin.
  - (iii) substances that favorably affect the color of ornamental fish or birds.
- (b) Flavoring compounds: substances that, when included in feedingstuffs, increase feed smell or palatability.

### **3. In the category “nutritional additives,” the following functional groups are included:**

- (a) Vitamins, pro-vitamins and chemically well-defined substances having similar effect.
- (b) Compounds of trace elements.
- (c) Amino acids, their salts and analogues.
- (d) Urea and its derivatives.

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### **4. In the category “zootechnical additives,” the following functional groups are included:**

- (a) Digestibility enhancers: substances that, when fed to animals, increase the digestibility of the diet, through action on target feed materials.
- (b) Gut-flora stabilizers: microorganisms or other chemically defined substances which, when fed to animals, have a positive effect on the gut flora.
- (c) Substances that favorably affect the environment.
- (d) Other zootechnical additives.

## REPORT REFERENCES

### CANADIAN REFERENCES:

#### **Feeds Act:**

<http://laws.justice.gc.ca/eng/F-9/20100809/page-0.html?rp2=HOME&rp3=SI&rp4=all&rp5=feeds%20act&rp9=cs&rp10=L&rp13=50#idhit1>

#### **Feeds Regulations:**

<http://laws.justice.gc.ca/eng/SOR-83-593/20100809/page-0.html?rp2=HOME&rp3=SI&rp4=all&rp5=feeds%20regulations&rp9=cr&rp10=L&rp13=50#idhit1>

#### **Health of Animals Act and Regulations:**

<http://laws.justice.gc.ca/eng/H-3.3/20100809/page-0.html?rp2=HOME&rp3=SI&rp4=all&rp5=health%20of%20animals&rp9=cs&rp10=L&rp13=50#idhit1>

#### **RG-1 Regulatory Guidance 1: Feed Registration Procedures and Labeling Standards:**

<http://www.inspection.gc.ca/english/anima/feebet/regdir/regdire.shtml>

#### **Foods and Drugs Act (Health Canada)**

<http://laws.justice.gc.ca/eng/F-27/index.html>

**Data Requirements For Product Safety Evaluations: Explanatory Notes T-3-141 Supplement 2 (also referred to as RG1, 2.5)**  
(not available on the internet)

#### **Regulatory Guidance/Industry Notices:**

<http://www.inspection.gc.ca/english/anima/feebet/polinde.shtml>

#### **Application for Feed Registration or Renewal:**

<http://www.inspection.gc.ca/english/for/pdf/c0009e.pdf>

**Standing Joint Committee on the Scrutiny of Regulations, SOR 97-6, May 7, 2009**  
(not available internet)

## **EUROPEAN UNION REFERENCES:**

### **Council Directive Feed Materials 96/25**

<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1996L0025:20030605:en:pdf>

### **Food Law Regulation (EC) No 178/2002**

[http://eur-lex.europa.eu/pri/en/oj/dat/2002/l\\_031/l\\_03120020201en00010024.pdf](http://eur-lex.europa.eu/pri/en/oj/dat/2002/l_031/l_03120020201en00010024.pdf)

### **Additives for Use in Animal Nutrition Regulation (EC) No 1831/2003**

<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:268:0029:0043:EN:PDF>

### **Community Register of Feed Additives Pursuant to Regulation (EC) No 1831/2003, Appendix 3 and 4**

[http://ec.europa.eu/food/food/animalnutrition/feedadditives/comm\\_register\\_feed\\_additives\\_1831-03.pdf](http://ec.europa.eu/food/food/animalnutrition/feedadditives/comm_register_feed_additives_1831-03.pdf)

### **Food Additive Applications Regulation (EC) No 429/2008**

<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:133:0001:0065:EN:PDF>

### **Market and Use of Feed Regulation (EC) No 767/2009**

<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:229:0001:0028:EN:PDF>

### **Commission Decision on Prohibited Substances 2004/217/EC**

<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:067:0031:0033:EN:PDF>

### **Directive 2001/82/EC Veterinary Medicinal Products**

[http://www.echamp.eu/fileadmin/user\\_upload/Regulation/Directive\\_2001-82-EC\\_-\\_Consolidated\\_Version\\_.pdf](http://www.echamp.eu/fileadmin/user_upload/Regulation/Directive_2001-82-EC_-_Consolidated_Version_.pdf)

### **Regulation (EC) No 1829/2003 Genetically Modified Food and Feed**

<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:268:0001:0023:EN:PDF>

### **Regulation (EC) No 1830/2003 Traceability and Labeling of Genetically Modified Organisms**

[http://eur-lex.europa.eu/LexUriServ/site/en/oj/2003/l\\_268/l\\_26820031018en00240028.pdf](http://eur-lex.europa.eu/LexUriServ/site/en/oj/2003/l_268/l_26820031018en00240028.pdf)

### **REGULATION (EC) No 1831/2003 Feed Hygiene**

[http://eur-lex.europa.eu/LexUriServ/site/en/oj/2005/l\\_035/l\\_03520050208en00010022.pdf](http://eur-lex.europa.eu/LexUriServ/site/en/oj/2003/l_268/l_26820031018en00240028.pdf)

## UNITED STATES REFERENCES

### **Federal Food Drug and Cosmetic Act (FFDCA):**

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticAct/FFDCA/default.htm>

### **MINOR USE MINOR SPECIES (MUMS) ACT**

[http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=108\\_cong\\_public\\_laws&docid=f:publ282.108.pdf](http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=108_cong_public_laws&docid=f:publ282.108.pdf)

### **Code of Federal Regulations (electronic copy)**

<http://ecfr.gpoaccess.gov/>

### **75 FR 31800; June 4, 2010 GRAS Notification**

<http://edocket.access.gpo.gov/2010/pdf/2010-13464.pdf>

### **66 FR 4706, January 18, 2001 Premarket Notice Concerning Bioengineered Foods**

<http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/Biotechnology/ucm096149.htm>

### **AAFCO 2010 Annual Meeting Ingredient Definition Committee Meeting Notes**

[http://www.aafco.org/Portals/0/minutes/idc\\_aug\\_2010.pdf](http://www.aafco.org/Portals/0/minutes/idc_aug_2010.pdf)

### **AAFCO PPT Safety Assessment for Feed Ingredients**

<http://www.aafco.org/Portals/0/powerpoint/aafcosafety.pdf>

### **AAFCO PPT Utility Assessment of Feed Ingredients**

[http://www.aafco.org/Portals/0/powerpoint/feed\\_ingredient\\_utility.pdf](http://www.aafco.org/Portals/0/powerpoint/feed_ingredient_utility.pdf)

### **AAFCO PPT Manufacturing Chemistry and Technical Additive Utility**

[http://www.aafco.org/Portals/0/powerpoint/aafco\\_presentation\\_mcc.pdf](http://www.aafco.org/Portals/0/powerpoint/aafco_presentation_mcc.pdf)

### **AAFCO PPT Enzyme Labeling**

[http://www.aafco.org/Portals/0/powerpoint/enzyme\\_labeling\\_for\\_feeds.pdf](http://www.aafco.org/Portals/0/powerpoint/enzyme_labeling_for_feeds.pdf)

### **AFIA Regulatory Training Course: Feed Ingredients, 2009**

(not available on the internet)

### **FDA Policy and Procedures Guide 1240.3605. Regulating Animal Foods with Drug Claims**

<http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/PoliciesProceduresManual/UCM046883.pdf>

**GFI 3: General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals**

<http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052180.pdf>

**GFI 33: Target Animal Safety Guidelines for New Animal Drugs 1989**  
(not available on the internet)

**CVM GFI #53 Evaluation of the Utility of Food Additives in Diet Fed to Aquatic Animals**

<http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm053413.htm>

**GFI 80: Studies to Evaluate the Utility of Anti-Salmonella Chemical Food Additives in Feeds**

<http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052407.pdf>

**GFI: Complementary and Alternative Medicine Products and their Regulation by the FDA**

<http://www.fda.gov/RegulatoryInformation/Guidances/ucm144657.htm>

**Memorandum of Understanding AAFCO and FDA**

<http://www.aaafco.org/Portals/0/Public/FINAL%20MOU-NUMBER%202-1.pdf>