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The Index of Legally Marketed Unapproved New Animal Drugs for Minor Species

Guidance for Industry

Draft Guidance

This guidance document is for comment purposes only.

Submit comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft guidance document, contact Dorothy Bailey, Office of Minor Use & Minor Species Animal Drug Development (HFV-50), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, (240) 402-0565, email: dorothy.bailey@fda.hhs.gov.

Additional copies of this draft guidance document may be requested from the Policy and Regulations Staff (HFV-6), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, and may be viewed on the Internet at https://www.fda.gov/AnimalVeterinary/default.htm or https://www.regulations.gov.

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Table of Contents

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Draft – Not for Implementation

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Guidance for Industry

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. PURPOSE

This guidance describes the process for adding a new animal drug to the Index of Legally Marketed Unapproved New Animal Drugs for Minor Species (the Index). The Index is available for new animal drugs intended for use in minor species; the Index is not available for drugs intended for minor use in major species.

Another guidance relating to the indexing process, a Small Entity Compliance Guide[1], is also available. That guidance answers some basic questions regarding the indexing process. It describes the specific requirements of the indexing regulations, which are found at Title 21, Code of Federal Regulations (CFR) part 516 subpart C.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required**.**

II. BACKGROUND

The Minor Use and Minor Species Animal Health Act of 2004 (MUMS Act) (Pub. L. No. 108-282) amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) to provide animal drug companies with incentives to develop new animal drugs for minor species and minor uses in major species, while still ensuring appropriate safeguards for animal and human health.

Congress recognized that the markets for new animal drugs for minor species and for minor uses in major species are so small that there often is insufficient economic incentive to motivate sponsors to pursue FDA approval of such products.

[1] See Guidance for Industry, Small Entities Compliance Guide, "The Index of Legally Marketed Unapproved New Animal Drugs for Minor Species" (GFI #201), available at https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM224589.pdf.

The MUMS Act encourages the development of animal drugs to treat minor species (species other than major species) or for minor uses (uncommon diseases or conditions) in major species (cattle, horses, swine, chickens, turkeys, dogs, and cats).

One of the incentives established by the MUMS Act is the Index of Legally Marketed Unapproved New Animal Drugs for Minor Species, also commonly referred to as "the Index." The Index consists of a list of legally marketed unapproved new animal drugs for minor species that meet the requirements of section 572 of the FD&C Act. We refer to the process of adding a new animal drug to the Index as "indexing." Indexing represents a new pathway for legally marketing unapproved new animal drugs.

In the Federal Register of December 6, 2007, FDA published final regulations establishing administrative procedures and criteria for listing a new animal drug for use in a minor species in the Index (72 FR 69108). These regulations, which are codified at 21 CFR part 516, subpart C, are administered by the Office of Minor Use and Minor Species Animal Drug Development (OMUMS) within FDA's Center for Veterinary Medicine (CVM). That office also maintains the Index, which is available to the public through FDA's website.[2]

III. THE INDEXING PROCESS

A. General

The Index provides a legal means for animal drug companies to market certain unapproved drugs for minor species. This is especially useful to veterinarians seeking to treat a variety of different species, such as ornamental fish, for which only a small number of approved animal drugs exist (if any). However, indexing is not available for all drugs intended for use in minor species. The Index is limited to drugs intended for use in nonfood-producing minor species and some early non-food life stages of food-producing minor species. The Index is not available for new animal drugs intended for minor use in major species.

In accordance with 21 CFR 516.157, the Index, as published on the FDA website, includes the following information for each indexed new animal drug:

1) The name and address of the person who holds the Index listing;
2) The name of the drug and the intended use and conditions of use for which it is indexed;
3) Links to product labeling and Freedom of Information (FOI) summary; and
4) Conditions and any limitations that FDA deems necessary regarding the use of the drug.

A person requesting that a new animal drug product be added to the Index is referred to as the "requestor" for that product. A requestor who has one or more new animal drug products indexed is referred to as a "holder" for those products (see 21 CFR 516.115). Thus, the holder of an Index listing may also be a requestor for a different Index listing.

[2] The Index of Legally Marketed Unapproved New Animal Drugs for Minor Species is available at https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM224589.pdf.

The holder of an Index listing is permitted to market the indexed new animal drug only in accordance with the provisions of the Index listing and the labeling accepted by the FDA. Extralabel use of an indexed product is prohibited (see sections 512(a)(4) and 572 (h)(1) of the FD&C Act).

The review process for indexed drugs includes an integrated process of agency and qualified expert panel review. For a new animal drug product intended for a particular use or uses, indexing involves a three-step process with each step involving a submission from the requestor and a review and decision by FDA. The 3 submissions from the requestor involve:

Step 1 - Requesting determination of eligibility for indexing;
Step 2 - Proposing a qualified expert panel (QEP) to evaluate target animal safety and effectiveness; and
Step 3 - Requesting addition to the Index.

A requestor initiates each of these steps. Once the indexing review process has begun, a requestor should not formally initiate the next step in the process until the preceding step is completed. The three steps in the process are discussed below.

In accordance with 21 CFR 516.171, all data and information submitted in support of the indexing of a particular product will be placed into, or included by reference into, an index file. FDA refers to this file as a Minor species Index File (MIF). The MIF is proprietary. FDA includes in the MIF all requestor submissions, including analyses, summaries and correspondence, along with supporting data and information; all FDA reviews, summaries and correspondence; and the report of the QEP. Additionally, the MIF will include data and information regarding any modification of the Index listing, changes in ownership, as well as records and reports relating to drug safety and adverse events submitted in accordance with 21 CFR 516.165.

At this time, requestors may send submissions to OMUMS either on paper or electronically via the FDA OMUMS Indexing eSubmitter process. To learn more about eSubmitter see the FDA website.

B. **Requesting Determination of Eligibility for Indexing (Step 1)**

The first step in the process for indexing a new animal drug intended for use in a minor species is for the requestor to ask for a determination from FDA that the drug is eligible for addition to the Index. In order to be eligible, a new animal drug must meet the statutory criteria for indexing (see 21 CFR 516.129).

A request for determination of eligibility of a new animal drug for indexing must contain all of the information required by that section, as follows:

1) Identification of the minor species or groups of minor species for which the new animal drug is intended;
2) Information regarding drug components and composition;
3) A statement of the intended use(s) of the new animal drug in the identified minor species or groups of minor species;
4) A statement of the conditions of use associated with the stated intended use(s) of the new animal drug, including the proposed dosage, route of administration, contraindications, warnings, and any other significant limitations associated with the intended use(s) of the new animal drug;
5) A brief discussion of the need for the new animal drug for the intended use(s);
6) An estimate of the anticipated annual distribution of the new animal drug, in terms of the total quantity of active ingredient, after indexing;
7) Information to establish that the new animal drug is intended for use:
   (i) in a minor species for which there is a reasonable certainty that the animal or edible products from the animal will not be consumed by humans or food-producing animals; or
   (ii) in a hatchery, tank, pond, or other similar contained man-made structure in an early non-food life stage of a food-producing minor species, and information to demonstrate food safety in accordance with the standards of section 512(d) of the FD&C Act and 21 CFR 514.111 (including, for an antimicrobial new animal drug, with respect to antimicrobial resistance);
8) A description of the methods used in, and the facilities and controls used for, the manufacture, processing and packing of the new animal drug sufficient to demonstrate that the requestor has established appropriate specifications for the manufacture and control of the new animal drug and that the requestor has an understanding of current good manufacturing practices;
9) Either a claim for categorical exclusion under 21 CFR 25.30 or 25.33 or an environmental assessment under 21 CFR 25.40;
10) Information sufficient to support the conclusion that the new animal drug is safe under section 512(d) of the FD&C Act with respect to individuals exposed to the new animal drug through its manufacture and use; and
11) The name and address of the contact person or permanent resident U.S. agent.

The request should be addressed to the Director of OMUMS. Indexing submissions must be dated and signed by the authorized contact person (for a non-US firm, this should be the U.S. agent) (see 21 CFR 516.129(c)).

See Appendix 1 for a sample letter that a requestor could use for a submission containing a request for determination of eligibility for indexing.

FDA may refuse to file submissions that lack any of the required information. In such cases, FDA will inform the requestor within 30 days as to what information is lacking (see 21 CFR

516.131). If a submission is complete, a response in the form of a letter granting or denying the request (the latter of which will explain the reasons for denial) will be prepared by OMUMS.

In the event of a denial of a request for a determination of eligibility, the requestor is entitled to appeal the decision through an informal conference with the Director of CVM or designee, as described in 21 CFR 516.123.

1. **The Intended Use**

A new animal drug is *not* eligible for indexing if it is intended for use in any animal species other than those minor species permitted by the FD&C Act (i.e., other than nonfood-producing minor species or an early non-food life stage of certain food-producing minor species). A new animal drug is *not* eligible for indexing if it is contained in, or is a product of, a transgenic animal.[3] A new animal drug is not eligible for indexing if the same drug in the same dosage form for the same intended use is already approved or conditionally approved (see 21 CFR 516.129(a) and 516.133(a)).

FDA defines the terms "same drug," "same dosage form," and "same intended use" in 21 CFR 516.3(b). These definitions apply to all of the implementing regulations for the MUMS Act, including those related to indexing.

The term "same drug" means "a MUMS drug for which designation, indexing, or conditional approval is sought that … contains the same active moiety as a prior designated, conditionally approved, or approved MUMS drug, even if the particular ester or salt … is not the same, it is considered the same drug; except that, if the prior MUMS drug is conditionally approved or approved and the second MUMS drug is shown to be functionally superior to the conditionally-approved or approved MUMS drug for the same intended use, it is not considered the same drug" (see 516.3(b)). Furthermore, "functionally superior" is defined in that same section, to include the nature and standard of proof necessary to establish superiority.

"Same dosage form" is based on dosage form *categories* as found in 21 CFR Subchapter E. OMUMS considers these categories to be different as follows:

21 CFR 520 – Oral dosage form new animal drugs
21 CFR 522 – Implantation dosage form new animal drugs
21 CFR 522 – Injectable dosage form new animal drugs
21 CFR 524 – Ophthalmic dosage form new animal drugs
21 CFR 524 – Topical dosage form new animal drugs
21 CFR 526 – Intramammary dosage form new animal drugs
21 CFR 529 – Certain other dosage form new animal drugs
21 CFR 558 – New animal drugs for use in animal feed

[3] FDA considers the term "transgenic animal" as used in this provision to be the equivalent of the term "genetically engineered animal" as used by FDA in Guidance for Industry #187, "Regulation of Intentionally Altered Genomic DNA in Animals," available at https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM113903.pdf.

Therefore, oral, implant, injectable, ophthalmic, topical, intramammary, other, and medicated animal feeds are different for this test. However, with the oral dosage form category, for example, tablets and suspensions are considered the same.

Appropriate subcategories of dosage forms for the "Certain other dosage forms" category will be determined as the need arises. For example, such subcategories may include inhalant anesthetics, intrauterine solutions, and immersion products for fish.

The term "same intended use" means "an intended use of a MUMS drug, for which designation, indexing, or conditional approval is sought, that is determined to be the same as (or not different from) a conditionally-approved, or approved intended use of a MUMS drug." The intended use includes both the animal species to be administered the drug and the disease or condition to be treated (see 516.3(b)).

"Same intended use" is established by comparing two intended uses and not just by comparing the labeling language used to state the intent. Two intended uses are considered the same if one of the intended uses falls completely within the scope of the other. For example, an intended use for "koi" would be within the scope of an intended use for "all ornamental fin fish." Two intended uses of a drug are not considered the same if they involve different intended species or different definable subpopulations (including "production classes") of a species.

In general, it should be easier for a QEP to determine the safety and effectiveness of a product with a narrower intended use. However, FDA recognizes the benefit of having a broader intended use in terms of conditions treated or species included. These factors should be considered when initially proposing an intended use in the determination of eligibility submission.

In accordance with 21 CFR 516.167(a)(1), after notice to the holder of the Index listing and an opportunity for an informal conference, FDA will remove an Index listing if the same drug in the same dosage form for the same intended use has been approved or conditionally approved.

2. **Required Safety and Manufacturing Information**

A request for determination of eligibility for indexing must address three primary aspects of product safety:

- Human food safety (for those new animal drugs intended for use in early non-food life stages of food-producing minor species);

- User safety evaluated in accordance with the standards in section 512 of the FD&C Act; and

- An environmental safety assessment (see 21 CFR 516.129(c)).

A summary of manufacturing processes must also be provided (see 21 CFR 516.129(c)(8)). Each of these areas is described in the following sections.

a. Human Food Safety

Eligibility for indexing requires that the treated animals do not end up as food for humans or other food-producing animals (see 516.111). Therefore, a determination of eligibility requires that the requestor show either that the animals intended to be treated:

- Belong to a species that is not customarily eaten in the U.S.;
- Belong to a species that are sometimes eaten but are kept under conditions that precludes their use as food; or
- Belong to the early non-food life stage of a food-producing minor species where that life stage is not eaten.

Table 1. Food Use Categories for Minor Species

Category	Example	Eligible for Indexing?
Nonfood-producing minor species	Ferrets, Mice, Lions	Yes
Food-producing minor species	Deer, Rabbit, Salmon	No
Early non-food life stage of food-producing minor species	Fish eggs that are not eaten, oyster larvae	Yes
Nonfood-producing minor species that are sometimes eaten	Bear and antelope in the wild	No
Nonfood-producing minor species with a reasonable certainty that they will not be eaten	Bear and antelope in zoos	Yes

Nonfood-producing Minor Species

Nonfood-producing minor species are defined largely by exclusion. These are species that do not meet the conditions of food-producing minor species as defined below. FDA generally considers that there is a reasonable certainty of no consumption of any member of a minor species that has not traditionally been consumed by humans or food-producing animals anywhere in the United States. Therefore, FDA would consider such species to be nonfood-producing minor species and to be eligible for indexing.

Food-producing Minor Species

FDA considers minor species to be food-producing species when some members of the species are bred, cultured, farmed, ranched, hunted, caught, trapped, or otherwise harvested for the purpose of having the animals or edible products of the animals *commercially distributed* for consumption by humans or food-producing animals in the United States. FDA generally will not consider a new animal drug intended for use in any member of such species (except when intended for use in an early non-food life stage) as eligible for indexing. Such minor species fall within, but are not necessarily limited to, the following commonly named species or species groups.

Table 2. Examples of Minor Species or Species Group by Common Name that FDA Considers to be Food-producing

Category	Minor Species or Species Group by Common Name
Mammals	Bison, deer, elk, goat, rabbit, sheep
Birds	Duck, emu, goose, guinea fowl, ostrich, partridge, pheasant, pigeon, quail, rhea
Reptiles	Alligator, turtle
Amphibians	Frog
Fish	Anchovy, arctic char, bass, bluefish, bonito, carp, catfish, cod, croaker, drum, eel, flounder, goosefish, grouper, haddock, hake, halibut, herring, mackerel, mullet, muskellunge, perch, pollock, pompano, porgie, rockfish, sablefish, salmon, sardines, shad, shark, skate, snapper, sole, sturgeon, swordfish, threadfin, tilapia, trout, tuna, walleye, whitefish
Crustaceans	Crab, crayfish, lobster, prawn, shrimp
Mollusks	Abalone, clam, mussel, oyster, octopus, scallop, snail, squid
Insects	Honey bee
Other	Sea urchin, sea cucumber

Note: This table is compiled from various sources identifying minor species commercially distributed for human consumption, but the list is not all-inclusive and may change over time.

Some minor species within a species group may meet the definition of food-producing minor species and others may not. For example, the commonly named species groups of duck, goose, turtle, frog, crab, shrimp, clam, or snail may include some species that are commercially distributed for consumption by humans or food-producing animals and others that are not. However, those minor species within a species group that are most likely to warrant drug treatment are also most likely to be food-producing minor species.

Early Non-food Life Stages of Food-producing Minor Species

The FD&C Act allows the indexing of new animal drugs that are intended for use in food-producing minor species only under very limited circumstances (see section 572(a)(B) of the FD&C Act). If a new animal drug is intended for use in a food-producing minor species there must be sufficient information to demonstrate it:

- Is for use in an early non-food life stage of the food-producing minor species;
- Is intended for use only in a hatchery, tank, pond, or other similar contained man-made structure; and
- Meets the food safety standards of section 512(d) of the FD&C Act (including, for an antimicrobial new animal drug, with respect to antimicrobial resistance) (see section 572 (a)(1) of the FD&C Act).

Examples of an early non-food life stage include catfish eggs and oyster larvae.

Reasonably certain not to be eaten

New animal drugs are eligible for indexing only if they are intended for use in a minor species for which there is a reasonable certainty that the animal or edible products from the animal will not be consumed by humans or food-producing animals (see 21 CFR 516.133(a)(2)(i)).

Not all animals that have traditionally been eaten by humans or food-producing animals in the United States are members of food-producing minor species as described above. This is due to the fact that the animals or edible products of the animals must be "commercially distributed" in order to meet the definition of a food-producing minor species. Therefore, some animals that are members of nonfood-producing minor species are sometimes eaten in the United States. Accordingly, indexed products cannot be intended for use in these animals unless there is a "reasonable certainty" that the treated animals or edible products from the treated animals will not be consumed by humans or food-producing animals, even if those species are otherwise considered nonfood-producing (see section 572(a)(1)(A) of the FD&C Act, 21 CFR 516.111).

A reasonable certainty that an animal will not be consumed can be established by the species of animal involved, by the circumstances associated with the intended purpose and maintenance of animals from a particular species that are involved, by labeling restrictions associated with the use of the new animal drug product involved, or by a combination of these factors.

There are a number of minor species that do not meet the definition of a food-producing minor species noted above, but may be hunted, caught, trapped, or otherwise "taken" and eaten by humans or food-producing animals in the U.S. For example, members of any wildlife species in the U.S. that are hunted, such as moose and squirrel. When members of such minor species (that are *not* food-producing minor species) are maintained in captivity (e.g., in a zoo), it is possible to establish with reasonable certainty that they will not be consumed by humans or food-producing animals.

Therefore, under appropriate conditions of intended use, an animal drug product limited to use in captive members of such minor species could be indexed.

FDA generally expects that it would not be possible to establish with reasonable certainty that free-ranging members of minor species or minor species raised in captivity and intended to be released (e.g., repopulating wildlife herds) that have traditionally been consumed in the U.S., and for which hunting, fishing, or trapping is licensed or otherwise permitted by various states, would not be consumed by humans or food-producing animals. Therefore, animal drugs intended for use in such animals would *not* be eligible for indexing.

There is a reasonable certainty of no consumption of such animals *only* when they are maintained in confinement in a zoo, laboratory or similar public or commercial facility and are *not* released or disposed of in any manner that may lead to their consumption by humans or food-producing animals *at any time* subsequent to their exposure to an indexed drug.

b. User safety

The indexing review process includes a provision for FDA to examine the safety of the new animal drug with respect to individuals who will be exposed to it during the drug's manufacture and use (see 21 CFR 516.129(c)(10)). The same user safety standards applicable to new animal drug approvals under section 512(d) of the FD&C Act also apply to new animal drug indexing eligibility determinations.

c. Environmental considerations

A request for eligibility for indexing must contain either an environmental assessment or sufficient information to support a categorical exclusion from the requirement to prepare an environmental assessment (see 21 CFR 516.129(c)(9)). The requirements for environmental assessments are defined in 21 CFR 25.40.

A request for determination of eligibility for indexing may be categorically excluded from the requirement to submit an environmental assessment (EA) if the drug and action meet one of the criteria for categorical exclusion described in 21 CFR 25.33. Two potential examples are drugs used in nonfood-producing animals (21 CFR 25.33(d)(1) and drugs used in minor species when the drug has previously been approved for use in another or the same species where similar animal management practices are used (21 CFR 25.33(d)(4)). When asking for a categorical exclusion from the requirement to prepare an EA, requestors should include a statement that they are not aware of any extraordinary circumstances that would preclude such an exclusion per 21 CFR 25.15(a) and (d), and also cite the specific paragraph of 21 CFR 25.33 that applies.

New animal drug products that are intended to be introduced into water for use in or on aquatic animals generally do not fall under categorically excluded actions defined in 21 CFR 25.33. Such new animal drug products generally require an EA. However, products intended for use only in aquaria or backyard ponds may be eligible for a categorical exclusion from the requirement for an EA.

Before claiming a categorical exclusion, the requestor is encouraged to contact the agency and discuss the specific indications and conditions of use.

In the process of preparing or reviewing an EA, it may become apparent that limitations need to be placed on the conditions of use, or that specific conditions of use need to be established to mitigate potential adverse effects on the environment. Therefore, FDA may recommend various labeling statements to mitigate such potential adverse effects.

d. Chemistry, manufacturing and controls information

A requestor must provide FDA with information regarding the components and composition of the new animal drug that is the subject of the eligibility request (see 21 516.129(c)(2)). Also, a requestor must submit a description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the new animal drug product (see section 572(c)(1)(D) of the FD&C Act, 21 CFR 516.129(c)(8)).

A requestor must provide a description of the components and composition of the new animal drug product and a summary of its manufacturing processes sufficient to:

- Demonstrate to the agency that the requestor has an understanding of the requirements of cGMPs, including the establishment of appropriate specifications for the manufacture and control of the new animal drug to be indexed (see 21 CFR 516.129(c)(8));

- Affirm the required commitment from the requestor that the new animal drug product to be indexed will be manufactured according to cGMPs (see 21 CFR 516.145(b)(7));

- Permit an evaluation of subsequent reported changes in formulation, changes in manufacturing process, or reported adverse drug experiences (see 21 CFR 516.161).

3. **Confidentiality of Information Regarding Eligibility for Indexing**

Information submitted by requestors in support of a determination of eligibility for indexing is confidential, in accordance with 21 CFR 516.171.

C. **Proposing A Qualified Expert Panel (Step 2)**

Once FDA makes a determination that a new animal drug is eligible for indexing, the next step is for FDA acceptance of a QEP that will assess relevant target animal safety and effectiveness information.

The QEP determines whether the benefits of using the new animal drug for the proposed use in a minor species outweigh its risks to the target animal. The QEP also takes into account the harm being caused by the absence of an approved or conditionally approved new animal drug for such use (see section 572(d)(2)(C) of the FD&C Act). QEPs operate external to FDA and are not subject to the Federal Advisory Committee Act, as amended, 5 U.S.C. App. 2 (section 572(d)(3) of the FD&C Act).

1. Procedures for Obtaining FDA Review of Qualified Expert Panels

The requestor must choose members for the QEP in accordance with selection criteria listed in the regulations at 21 CFR 516.141(b) and submit information about the proposed QEP members to FDA in accordance with 21 CFR 516.141(a). Specifically, the requestor must submit to FDA, in writing, the names and addresses of the proposed QEP members and sufficient information about each member's qualifications to permit FDA to determine whether the individual QEP members and the QEP as a whole meet the selection criteria (see 21 CFR 516.141(c)(2)). Appendix 2 provides an example of a letter that a requestor could use when proposing QEP members for FDA's consideration.

In accordance with 21 CFR 516.141(b)(4), a QEP must consist of at least three members. FDA considers that, in order to meet the requirements of 21 CFR 516.141(b)(5), a QEP should contain at least one member thoroughly familiar with disease conditions and husbandry practices in the United States, typically by virtue of training and/or substantial experience. The chair of the QEP should be a U.S. citizen residing in the United States.

FDA may request additional information from the requestor or proposed members, may request additional experts for the QEP, or may determine that proposed members do not meet the selection criteria (see 21 CFR 516.141).

FDA will prepare a response to the requestor in the form of a letter accepting or rejecting the proposed QEP. Letters of rejection will identify issues of concern. In the event of FDA rejection of a QEP, the requestor is entitled to appeal the decision through an informal conference with the Director of CVM or their designee (see 21 CFR 516.141(d)(2), 516.123).

2. Determination of the Acceptability of Proposed Qualified Expert Panels

In order to permit FDA to determine whether a proposed QEP is acceptable, the requestor must obtain and submit to FDA all required information in 21 CFR 516.141(b) and (c). In accordance with 21 CFR 516.141(b)(2), each proposed QEP member must certify that he or she has a working knowledge of section 572 of the FD&C Act (the indexing provisions of the statute) and 21 CFR part 516 subpart C. In addition, each proposed QEP member must certify that he or she has read and understood a written statement provided by the requestor, stating his or her duties and responsibilities with respect to reviewing the new animal drug proposed for addition to the Index.

An example of such a statement follows:

> I certify that I have a working knowledge of section 572 of the FD&C Act (the indexing provisions of the statute) and 21 CFR part 516 subpart C.
> I have read and understand the written statement provided by [the requestor] stating my duties and responsibilities with respect to reviewing the new animal drug proposed for addition to the Index.

In accordance with 21 CFR 516.141(c)(2), the requestor must submit the names and addresses of each of the proposed QEP members and information about the qualifications of the proposed QEP members sufficient for FDA to determine that the QEP meets the selection criteria.

This should include information demonstrating that each potential QEP member is qualified by training and experience to evaluate the target animal safety and effectiveness of the new animal drug under consideration. This information would likely consist of a comprehensive curriculum vitae or similar document (see 21 CFR 516.141(c)(1)(iv)). Each QEP member does not need to be qualified to evaluate all aspects of the target animal safety and effectiveness of the drug, but the QEP as a whole must be qualified to evaluate all aspects of the drug's target animal safety and effectiveness (see 21 CFR 516.141(b)(5)).

Requestors need to notify each QEP member of the requirement to submit, in writing, conflict of interest information described in paragraph (g)(3) of 21 CFR 516.141. QEP members may submit this information to CVM directly or through the requestor.

Each QEP member must respond specifically to the issues that are addressed in 21 CFR 516.141(g)(3). That is, each QEP member must address each of the issues shown in the example below. A simple "none," or "not applicable" may be a satisfactory answer. QEP members should supply only information that pertains to an activity, relationship, or holding relevant to the new animal drug that is the subject of the review of the QEP.

A conflict of interest statement similar to the following would be satisfactory:

To permit FDA to make a decision regarding potential conflict of interest, I submit the following information relating to me, my spouse, our minor children, my general partners, or any organizations in which I serve as an officer, director, trustee, general partner or employee, regarding the following issues to the extent that they are, in any way, relevant to the subject of the review of the qualified expert panel:

1. *Investments (for example, stocks, bonds, retirement plans, trusts, partnerships, sector funds, etc.), including for each the following: Name of the firm, type of investment, owner (self, spouse, etc.), number of shares / current value.*
   None _____ Not applicable _____ Attached _____
2. *Employment (full or part time, current or under negotiation), including for each the following: Name of the firm, relationship (self, spouse, etc.), position in firm, date employment or negotiation began.*
   None _____ Not applicable _____ Attached _____
3. *Consultant/advisor (current or under negotiation), including for each the following: Name of the firm, topic/issue, amount received, date initiated.*
   None _____ Not applicable _____ Attached _____
4. *Contracts, grants, Cooperative Research and Development Agreements (CRADAs) (current or under negotiation), including for each the following: Type of agreement, product under study and indications, amount of remuneration (institution/self), time period, sponsor (government, firm, institution, individual), role of the person (site*

investigator, principal investigator, co-investigator, partner, no involvement, other), awardee.
None _____ Not applicable _____ Attached _____

5. *Patents/royalties/trademarks, including for each the following: Description, name of firm involved, income received.*
   None _____ Not applicable _____ Attached _____
6. *Expert witness (last 12 months or under negotiation), including for each the following: For or against, name of firm, issue, amount received.*
   None _____ Not applicable _____ Attached _____
7. *Speaking/writing (last 12 months or under negotiation), including for each the following: Firm, topic/issue, amount received (honorarium/travel), date.*
   None _____ Not applicable _____ Attached _____
8. *Whether there are any other involvements (other kinds of relationships) that would give the appearance of a conflict of interest which have not been described in the paragraphs above.*
   None _____ Not applicable _____ Attached _____

The last paragraph of each QEP member's conflict of interest statement must include a statement certifying the following:

1) That all information submitted is true and complete to the best of their knowledge (516.141(g)(3)(xi));

2) That they have read and understand their obligations as an QEP member (516.141(b)(2)); and

3) That they will notify FDA and the requestor of any change in their conflict of interest status (516.141(e)(7)).

The following is an example of a certification statement:

> I certify that: all information submitted is true and complete to the best of my knowledge; I have read and understand my obligations as a qualified expert panel member; and that I will notify FDA and [the requestor] of any change in my conflict of interest status.

The QEP member should sign and date the certification statement.

The fact that a QEP member may receive a reasonable fee for services as a member of the QEP, provided that the fee is no more than commensurate with the value of the time that the member devotes to the review process, does not constitute a conflict of interest or the appearance of a conflict of interest (see 21 CFR 516.141(g)(4)).

To be clear, QEP members only need to report information that is relevant to the subject of the review of the QEP. They do not need to report stocks, other investments, etc., that have no relevance to the work of the QEP.

3. **Confidentiality of Information Regarding QEP Members**

The confidentiality of information submitted by requestors and proposed QEP members will be maintained in accordance with the provisions of 21 CFR 516.171.

Individual requestors are free to release whatever information they choose regarding proposed QEP members in accordance with whatever confidentiality agreement they reach with those members. Any expert who has qualified for service on a QEP is free to make information regarding the nature and extent of their expertise or their willingness to serve on QEPs available to any extent they wish. FDA will not establish a list of experts who have qualified to serve on QEPs and will not respond to specific requests for information regarding potential QEP members from requestors. However, FDA will make available an FOI summary for each new animal drug appearing in the Index that will identify the QEP members who reviewed and recommended indexing of that particular new animal drug.

4. **QEP Responsibilities**

Following acceptance of the QEP by FDA, the requestor provides the QEP with the information described in 21 CFR 516.141, including full copies of all publicly-available literature to be considered by the QEP. The QEP thoroughly reviews and discusses all available target animal safety and effectiveness information relevant to the proposed intended use (including anecdotal information from the QEP members).

The responsibilities for the QEP and the leader of the QEP are listed in 21 CFR 516.141(e) and (f).

The QEP drafts a written report containing a description of the QEP's deliberative process and a recommendation on safety and effectiveness relevant to the proposed intended use. In order for the drug to be added to the Index, the panel must unanimously conclude that the benefits of using the new animal drug for the proposed use outweigh its risk to the target animal, taking into account the harm being caused by the absence of an approved or conditionally approved new animal drug for the minor species in question.

In addition, the report must:

- Provide draft labeling that includes all conditions of use and limitations of use of the new animal drug deemed necessary by the panel to assure that the benefits of use of the new animal drug outweigh the risks, or provide narrative information from which such labeling can be written by the requestor.

- Include the QEP's recommendation regarding whether the new animal drug should be limited to use under the professional supervision of a licensed veterinarian.

- Be signed or otherwise approved in writing by each member of the QEP in accordance with 21 CFR 516.141.

The completed written report is provided to the requestor for inclusion in the submission requesting addition of the product to the Index (see 21 CFR 516.143).

D. Requesting Addition of a Product to the Index (Step 3)

Provided the first two steps are completed successfully, the third step in the process is for the requestor to submit a letter requesting to have the new animal drug product added to the Index.

1. Contents of a Request for Addition to the Index

The content and format of a request for the addition of a new animal drug to the Index must meet all of the requirements of 21 CFR 516.145 "Content and format of a request for addition to the index", as follows:

a) A copy of FDA's determination of eligibility issued under 21 CFR 516.137;
b) A copy of FDA's written determination that the proposed qualified expert panel meets the selection criteria provided for in 21 CFR 516.141(b);
c) A written report that meets the requirements of 21 CFR 516.143;
d) A proposed index entry that contains the information described in 21 CFR 516.157;
e) Proposed labeling, including representative labeling proposed to be used for Type B and Type C medicated feeds if the drug is intended for use in the manufacture of medicated feeds;
f) Anticipated annual distribution of the new animal drug, in terms of the total quantity of active ingredient, after indexing;
g) A written commitment to manufacture the new animal drug and animal feeds bearing or containing such new animal drug according to current good manufacturing practices;
h) A written commitment to label, distribute and promote the new animal drug only in accordance with the index entry;
i) The name and address of the contact person or permanent-resident U.S. agent; and
j) A draft FOI summary which includes the following information:
    i. A general information section that contains the name and address of the requestor and a description of the drug, route of administration, indications, and recommended dosage;
    ii. A list of the names and affiliations of the members of the qualified expert panel, not including their addresses or contact information;
    iii. A summary of the findings of the qualified expert panel concerning the target animal safety and effectiveness of the drug;
    iv. Citations of all publicly-available literature considered by the expert panel;
    v. For an early non-food life stage of a food-producing minor species animal, a human food safety summary.

A sample letter that a requestor could use to ask FDA to add a new animal drug product to the Index is provided in Appendix 3.

To facilitate FDA review, it is very helpful if the request includes the first two pages of each literature article considered by the QEP. If needed, the Agency can request that any information provided to the QEP in support of indexing a new animal drug product be submitted for review (see 21 CFR 516.145(c)).

FDA may refuse to file submissions that lack any of the required information (see 21 CFR 516.147).

If FDA determines that the QEP's report demonstrates that the QEP conducted a thorough review of available information that meets the requirements of the regulations, and that labeling proposed for the product is satisfactory in *all* respects, FDA will grant the request for addition to the Index (see 21 CFR 516.151).

If the proposed labeling or the report of the QEP is insufficient, FDA will not grant the request for addition to the Index. Upon a determination that the request for addition to the Index contains insufficient information, FDA will inform the requestor in writing as to what information is lacking (see 21 CFR 516.149).

In accordance with the process that FDA has established to implement the indexing provisions of the FD&C Act and its implementing regulations, FDA may request revised labeling or additional information from the requestor or QEP. In the event FDA denies a request for addition to the Index, the requestor is entitled to appeal the decision through an informal conference with the Director of CVM or his or her designee (see 21 CFR 516.153(b)).

2. **Confidentiality of Information**

Information submitted by requestors in support of a request for addition of a new animal drug product to the Index is considered to be confidential in accordance with the provisions of 21 CFR 516.171.

As directed in the FD&C Act, FDA makes the following information publicly available in the Index listing for each listed drug:

a. The name and address of the person who holds the Index listing;
b. The name of the drug and the intended use and conditions of use for which it is indexed;
c. Product labeling; and
d. Conditions and any limitations that FDA deems necessary regarding the use of the drug (see section 572(e)(1) of the FD&C Act and its implementing regulations at 21 CFR 516.157).

Section 301(j) of the FD&C Act prohibits the release by the FDA of any information acquired under authority of section 572 of the FD&C Act concerning any method or process which as a

trade secret is entitled to protection except when required by Congress or the Courts under certain conditions.

Also, section 572(j) of the FD&C Act establishes conditions under which "[s]afety and effectiveness data and information which has been submitted in support of a request for a new animal drug to be indexed under this section and which has not been previously disclosed to the public shall be made available to the public, upon request, unless extraordinary circumstances are shown. . . ."

In accordance with 21 CFR 516.171(e)(2), the indexing process requires the preparation and subsequent public availability of a summary of the safety and effectiveness data and information submitted with or incorporated by reference in the Index file. FDA will make a summary of this information publicly available in a final FOI summary that is based upon the draft FOI summary provided by the requestor (see 21 CFR 516.145(b)(10).

Prior to public notice of the indexing of a new animal drug, FDA will not make public the existence of an MIF for the new animal drug, unless previously publicly disclosed by the requestor (see 21 CFR 516.171(b)). After indexing of the subject product, an analysis and associated summary of publicly available data or information by the requestor or by the QEP is considered confidential commercial information. Portions of agency reviews dealing with such information may be considered confidential commercial information. Portions of correspondence from the requestor or the agency regarding such information may be considered confidential commercial information.

The same standards concerning disclosure of confidential commercial information that apply to NADAs apply to MIFs (see 21 CFR 20.61).

Therefore, sponsors of investigational new animal drug (INAD) files and/or NADAs that may also be requestors of indexed products do not need to be concerned that either the submission or use of data or information to support indexing will compromise subsequent confidentiality with respect to new animal drug approval.

IV. LABELING

A. General principles

Labeling of indexed products must meet all of the general labeling requirements under section 502 of the FD&C Act and applicable provisions of 21 CFR part 201. Once FDA has accepted labeling, only that labeling may be used for marketing the indexed drug product.

When determining eligibility for indexing, FDA determines whether the intended use of a product meets the human food, user, and environmental safety standards of sections 512 and 572(a)(1)(B) and (c)(1)(F) of the FD&C Act. FDA may ask that requestors implement changes to proposed labeling in order to address human food safety, user safety, or environmental safety concerns. FDA may deny a request for addition to the Index if such changes are not included in the labeling for the new animal drug.

The QEP evaluates the available target animal safety and effectiveness information and provides draft labeling or comments and revisions to draft labeling or provides information from which the requestor can write labeling. Such information includes conditions and limitations of use that the QEP deems necessary to assure that the benefits of the new animal drug for its proposed use outweigh its risks for the target animal (see 21 CFR 516.143(f)(1)). However, while the QEP provides an opinion, FDA ultimately determines whether the new animal drug meets this standard, as well as whether the requestor's proposed labeling adequately captures the QEP's recommendations and otherwise adheres to the requirements of the FD&C Act.

B. **Labeling Statements**

Section 572(h)(1) of the FD&C Act states that the following statements must appear "prominently and conspicuously" on the labeling of every indexed product:

> NOT APPROVED BY FDA.—Legally marketed as an FDA Indexed product. Extra-label use is prohibited.

The following statement should appear immediately following the previous statutorily required statement:

> NOTE: In order to be legally marketed, an animal drug product intended for a minor species must be Approved, Conditionally Approved, or Indexed by the FDA. THIS PRODUCT IS INDEXED – MIF [file number].

In accordance with 21 CFR 516.155(a), any indexed product that is *not* intended for use in an early, non-food life stage of a minor species, *must* "prominently and conspicuously" bear the following statement:

> This product is not to be used in animals intended for use as food for humans or other animals.

This statement can, but is not required to, directly follow the required labeling statements previously discussed.

C. **Additional Human Food Safety Labeling Statements**

In accordance with the requirements of section 572 of the FD&C Act, if a proposed intended use is sufficiently broad to imply use in food-producing minor species (other than early, non-food life stages of those species), the intended use should explicitly state that it excludes use in food-producing minor species. Such a statement is in addition to the labeling statements described above.

Similarly, when the labeling of an indexed product intended for use in minor species that are maintained in captivity as laboratory animals or as zoo animals is sufficiently broad to imply use in food-producing minor species, the intended use should state that it excludes use in food-producing minor species. Such a statement is in addition to the required labeling statement described above.

New animal drugs intended for use in members of nonfood-producing minor species that could possibly be eaten that are *permanently* maintained in confinement are eligible for indexing. Thus, labeling in this circumstance need not exclude *use* in such nonfood-producing minor species, *provided* the intended use explicitly precludes *release or disposal* of such animals in any manner that may lead to their consumption by humans or food-producing animals *at any time* subsequent to their exposure to the indexed drug.

The following is an example of a potential statement of intended use for an indexed product for use in zoo (or laboratory) animals:

> For immobilization of captive minor species hoof stock, excluding any animals that may become eligible for consumption by humans or food-producing animals.

The FDA may require the full definition of "food-producing minor species" (see section III.B.2.a of this guidance) on the label but it need not be part of the indications for use. In some cases, FDA may allow an alternative statement that describes the limitations for use in accordance with the indications for use. For example, a drug indexed for use in pet birds might have a label statement such as:

> Use of this product is prohibited in food-producing species such as chickens, turkeys, ducks, pigeons, and game birds.

Because the FD&C Act prohibits use of indexed drugs in food-producing minor species or in other minor species that may be consumed by humans or food-producing animals, the indexing of products intended for use in many wildlife species is unlikely to be permitted.

Most of the wildlife species that warrant managing in the wild, and which would, therefore, support the development of various drugs otherwise eligible for indexing, have traditionally been consumed by humans or food-producing animals somewhere in the U.S. Therefore, in most cases, an indexed product for use in wildlife would be restricted to a few specifically identified minor species with labeling exclusions for any other uses.

The following is an example of a potential statement of intended use for an indexed product for use in wildlife:

> For the immobilization of mountain lions and bobcats. Not for use in animals that may be consumed by humans or food-producing animals.

D. **Labeling Related to Environmental Safety**

In the process of preparing or reviewing an EA, it may become apparent that limitations need to be placed on conditions of use or that specific conditions of use need to be established to mitigate potential adverse effects on the environment and would require preparation of an environmental impact statement (see 21 CFR 25.40(e)). FDA may require various labeling statements to mitigate such potential adverse effects, where applicable.

E. **Labeling Related to User Safety**

In accordance with section 572(c)(2) of the FD&C Act and its implementing regulations at 21 CFR 516.133, an indexed new animal drug must be "safe with respect to individuals exposed to the new animal drug through its manufacture or use." FDA may require labeling statements relating to user safety in order to allow it to make this user safety finding.

V. SPECIAL CONSIDERATIONS

A. **Collective Gathering of Information by Multiple Parties**

While the FD&C Act does not provide any marketing exclusivity with respect to indexed products, it does require that new animal drugs be indexed on a specific product basis (see section 572(c) of the FD&C Act). However, the FD&C Act does not require that all information supporting such indexing be gathered and submitted by individual requestors. The agency recognizes that there could be economic or other benefits associated with the collective gathering of information by multiple persons in support of the indexing of similar new animal drug products.

Requestors who wish to index a group of similar new animal drug products can collectively gather information to support requests for determination of eligibility for indexing. Once this information is gathered, each requestor should submit a separate request for determination for eligibility to their MIF.

FDA may allow requestors to share a QEP that will review the safety and effectiveness of a group of similar new animal drug products for similar uses. However, each requestor should file a submission to their own MIF for acceptance of the shared QEP. Requestors can collectively gather available safety and effectiveness information for review by the shared QEP. While a shared QEP is required to reach a conclusion regarding each specific product reviewed and to provide that conclusion in a written report to the appropriate requestor, a shared QEP's review process could be facilitated by concurrently reviewing a group of related products that are largely supported by the same information. Once review of the group of products is completed by the shared QEP, each requestor should submit the report written by the shared QEP specific to their product to their MIF as part of a request for addition to the Index.

B. **Indexing Combination Drugs**

It is possible to index combinations of new animal drugs. However, there are restrictions in the FD&C Act that limit the ability of the agency to index specific combinations of new animal drugs.

A combination product can be indexed if none of the components are approved or conditionally approved for the same intended use. However, requestors should keep in mind that combination products may pose challenges for the agency and for the QEP and, therefore, may be considerably more difficult to index than products containing a single active ingredient.

VI. MODIFICATIONS TO AN INDEXED DRUG

After a drug has been added to the Index, there are certain modifications to the index listing that may be requested. A modification to an indexed drug cannot cause the drug to be a different drug, different combination of drugs, or different dosage form. These types of changes require a new index listing. There are three types of modifications to an indexed drug which are explained in detail in 21 CFR 516.161 and summarized below:

A. **Urgent Changes**

An urgent change is a modification to an indexed drug or its labeling that should be made as soon as possible. The request to modify the indexed drug should be submitted to FDA for review at the same time the change is being made. The request for modification must contain enough information to permit FDA to determine the need for the change and whether the modification is appropriate to address the need. For further information on the content of a request for an urgent change see 21 CFR 516.161(b)(1)(iii). The following modifications are considered urgent changes:

- The inclusion of additional warning, contraindication, side effect, or cautionary information to package labeling, promotional labeling, or prescription drug advertising.
- The deletion from package labeling, promotional labeling, or drug advertising of false, misleading, or unsupported indications for use or claims for effectiveness.
- Changes in manufacturing methods or controls required to correct product or manufacturing defects that may result in serious adverse drug events.

B. **Significant Changes**

A significant change is a modification to an indexed drug or its labeling that can only be made after a request has been submitted to and granted by the FDA. Modifications that are considered significant changes must go through the same three-step review process as an original index listing. This means that a request for determination for eligibility must be granted and a QEP must be accepted prior to submitting the request for the modification. For further information regarding this type of modification (see 21 CFR 516.161(b)(2)). The following modifications are considered significant changes:

1. Addition of an intended use.
2. Addition of a species.
3. Addition or alteration of an active ingredient.
4. Alteration of dose or dosage regimen.
5. Alteration of prescription or over-the-counter status.

C. **Minor Changes**

A minor change is any modification other than those described as an urgent change or a significant change. This type of modification should be submitted as part of the annual indexed drug experience report in accordance with 21 CFR 516.161(b)(3).

VII. POST INDEXING RECORDS AND REPORTS

The holder of an index listing is responsible for filing reports on a recurring basis following the addition of the product to the Index. These reports are fully described in 21 CFR 516.165 and summarized as follows:

A. **Recordkeeping requirements (21 CFR 516.165(b))**

- Records: The holder must keep up-to-date files containing complete records of all information regarding the safety and effectiveness of the indexed product. This includes information from both foreign and domestic sources.

- Access: The holder must permit authorized FDA personnel to view, copy, and verify any of these records.

B. **Reporting requirements (21 CFR 516.165(c))**

Reports must be submitted in a timely manner appropriate for the type of report. These are summarized below and more fully described in the regulations.

1. **Annual Indexed Drug Experience Reports**

A sample format for the Annual Indexed Drug Experience Report is included in the appendix to assist the holder in providing the required information. The holder may use this template or any other that provides the same information.

2. **Three-day, Fifteen-day, or Periodic Adverse Experience Reports**

A sample format for adverse experience reports is included in the appendix to assist the holder in providing the required information. A holder may use this template to submit a 3-day, 15-day, or Periodic Report. A holder may also use the Form FDA 1932a or the longer Form FDA 1932 to submit these reports. Electronic versions of both forms are available on the FDA website. The holder may use these forms or any other format that provides the same information.

a. Three-day Indexed Drug Field Alert Report (516.165(c)(1))

This report is the means by which the holder notifies the FDA of product or manufacturing defects that could lead to serious adverse drug events. This report should be directed to the nearest FDA District Office or resident post. As the title states, this must be done within 3 days of the discovery of the problem. The initial report may be by telephone or electronic communication with a follow up in writing.

b. Fifteen-day Indexed Drug Field Alert Report (516.165(c)(2))

This report must be submitted within 15 days of receipt of any information associated with a serious or unexpected adverse drug experience. This must be reported regardless of the source of the information. This report should be submitted to OMUMS. The report must be in writing and clearly labeled on the envelope.

c. Annual Indexed Drug Experience Report (516.165(c)(3))

This report is due to OMUMS within 60 days after the anniversary of the date the product was added to the Index and must include required information for the full year. Any information provided previously should be so identified. The information to be included is fully described in the regulation cited above and is included on the sample report included in the Appendix to this guidance.

The information required covers:

- The number of distributed units of each size, strength, or potency;
- Any changes to labeling since the previous report;
- A summary of any changes to the manufacturing, processing, or packing of the product;
- Any nonclinical laboratory studies and clinical data not previously reported;
- Adverse drug experiences not previously reported; and
- Any other information pertinent to safety or effectiveness not previously reported under this section.

d. Distributor's Statement (516.165(c)(4))

If the holder markets the product through one or more distributors, the holder must submit a report including specific labeling information and a signed statement by the distributor. The statements to be included are included in the regulation. These must be provided to OMUMS at the time the distribution begins.

VIII. REMOVAL FROM THE INDEX

There are several reasons that FDA could take action to remove a product from the Index. These are fully described in the regulations (see 21 CFR 516.167(a)). In summary these are:

- The same drug in the same dosage form with the same intended use is approved or conditionally approved;
- The expert panel failed to meet requirements;
- FDA finds that, based on new information, the risks outweigh the benefits;
- Failure to meet specified requirements of eligibility for indexing;
- Failure to comply with current Good Manufacturing Practices;
- Failure to label, distribute, or promote the product in accordance with the Index listing;
- Failure to observe conditions and limitations of use in the Index listing; or
- Use of untrue statements of material fact in support of the request to add the product to the Index.

The holder will be notified and offered an opportunity for an informal conference before an action is taken for any of these reasons.

The FDA can remove part of an Index listing if that would resolve a safety or effectiveness issue (see 21 CFR 516.167(b)).

FDA can also suspend an Index listing without prior notice if there is reasonable probability that use of the drug would present a health risk to animals or people. In such cases, the opportunity for an informal conference would come after the action was taken (see 21 CFR 516.167(c)).

IX. APPENDICES

Appendix 1: Sample Letter
Request for Determination of Eligibility for Indexing

Insert Current Date

Director
Office of Minor Use & Minor Species
Animal Drug Development (OMUMS)
FDA Center for Veterinary Medicine
7500 Standish Place, HFV-50
Rockville, MD 20855

Request for Determination of Eligibility for Indexing

Dear Director:

Insert Company Name is submitting a signed copy of a request for determination of eligibility for indexing for *Insert Drug Proprietary Name* (*Insert Drug Established Name*) for *Insert Intended Use*.

In accordance with 21 CFR 516.129, we are submitting the following information in support of this request:

1. Identification of the minor species or groups of minor species for which the new animal drug is intended;
2. A statement whether the new animal drug is contained in, or a product of, a transgenic (i.e., genetically engineered) animal;
3. Information regarding drug components and composition;
4. A statement of the intended use of the new animal drug in the identified minor species;
5. A statement of the proposed conditions of use of the new animal drug, including the proposed dosage, route of administration, contraindications, warnings, and any other significant limitations associated with the intended use(s) of the new animal drug;
6. A statement describing the need for the new animal drug for the intended use;
7. An estimate of the anticipated annual distribution of the new animal drug in terms of the total quantity of active ingredient, after indexing;
8. Information to establish that the new animal drug is intended for use:
    - In a minor species for which there is a reasonable certainty that the animal or edible products from the animal will not be consumed by humans or food-producing animals, or;
    - In or on an early non-food life stage of a food-producing minor species residing in a hatchery, tank, pond, or other similar contained man-made structure, with information to demonstrate food safety in accordance with the standards of sections 512(d) of

FD&C Act and 21 CFR 514.111 (including, for an antimicrobial new animal drug, with respect to antimicrobial resistance);

9. A description of the methods used in, and the facilities and controls used for, the manufacture, processing and packing of the new animal drug sufficient to demonstrate that the requestor has established appropriate specifications for the manufacture and control of the new animal drug and that the requestor has an understanding of current good manufacturing practices;
10. An environmental assessment; or claim for categorical exclusion from the requirement of preparing an environmental assessment along with a statement as to whether you are aware of extraordinary circumstances that preclude such an exclusion;
11. Information to support the conclusion that the new animal drug is safe under 512(d) of the FD&C Act with respect to individuals exposed to the new animal drug through its manufacture and use; and
12. The name and address of the contact person or permanent-resident U.S. agent.

If you have any questions, please contact me at *Insert Phone Number(s).*

Insert Signature Block

Please note: *Letters should be addressed to the Director of OMUMS, but the submission packages containing those letters should be mailed to the FDA/CVM Document Control Unit, HFV-199, 7500 Standish Place, Rockville, Maryland 20855.*

Appendix 2: Sample Letter
Re: MIF Z-900XXX Proposed Qualified Expert Panel

Insert Current Date

Director
Office of Minor Use & Minor Species
Animal Drug Development (OMUMS)
FDA Center for Veterinary Medicine
7500 Standish Place, HFV-50
Rockville, MD 20855

Re: MIF Z-900*XXX* Proposed Qualified Expert Panel

Dear Director:

Insert Company Name is submitting a signed copy of our proposal for a qualified expert panel to evaluate the target animal safety and effectiveness of *Insert Drug Proprietary Name* (*Insert Drug Established Name*) for *Insert Intended Use*.

In accordance with 21 CFR 516.141, we have:

1. Chosen members for the qualified expert panel in accordance with the selection criteria listed in 21 CFR 516.141(b);
2. Provided each potential panel member a copy of section 572 of the Federal Food, Drug and Cosmetic Act and of 21 CFR part 516 subpart C; and obtained certification that each proposed panel member has a working knowledge of this information;
3. Provided each potential qualified expert panel member a written statement describing the purpose and scope of his or her participation on the qualified expert panel and obtained certification that he or she has read and understood the information;
4. Obtained information (enclosed) from each potential qualified expert panel member demonstrating that he or she is qualified by training and experience to evaluate the target animal safety and effectiveness of the new animal drug under consideration; and
5. Notified each potential qualified expert panel member that he or she must submit information relating to potential conflict of interest either directly to FDA, or if the panel member chooses, through our firm to FDA, in a timely manner as required in 21 CFR 516.141(e)(6).

We also agree to immediately notify FDA if we believe a qualified expert panel member no longer meets the selection criteria listed in 21 CFR 516.141(b) or is otherwise not in compliance with the requirements of this section.

If you have any questions, please contact me at *Insert Phone Number(s)*.

Insert Signature Block

X enclosures

Please note: *the letter should be addressed to the Director, Office of Minor Use & Minor Species Animal Drug Development, HFV-50, Center for Veterinary Medicine, 7500 Standish Place, Rockville, Maryland, 20855. However, the package containing the letter should be mailed to the FDA/CVM Document Control Unit, HFV-199, 7500 Standish Place, Rockville, Maryland 20855.*

Appendix 3: Sample Letter
Re: MIF Z-900XXX Request for Addition to the Index

Insert Current Date

Director
Office of Minor Use & Minor Species
Animal Drug Development (OMUMS)
FDA Center for Veterinary Medicine
7500 Standish Place, HFV-50
Rockville, MD 20855

Re: MIF Z-900*XXX* Request for Addition to the Index

Dear Director:

Insert Company Name is submitting a signed copy of our request for addition to the Index of *Insert Drug Proprietary Name* (*Insert Drug Established Name*) for *Insert Intended Use*.

In accordance with 21 CFR 516.145, we are submitting the following:

1. A copy of FDA's determination of eligibility letter;
2. A copy of FDA's letter accepting the proposed qualified expert panel;
3. A written report that meets the requirements of 21 CFR 516.143;
4. A proposed Index entry that contains the information described in 21 CFR 516.157;
5. Proposed labeling, including representative labeling proposed to be used for Type B and Type C medicated feeds if the drug is intended for use in the manufacture of medicated feeds;
6. Anticipated annual distribution of the new animal drug, in terms of the total quantity of active ingredient, after indexing;
7. A written commitment to manufacture the new animal drug (including animal feeds bearing or containing such new animal drug, if applicable) according to current good manufacturing practices as described in 21 CFR part 211 for finished pharmaceuticals, 21 CFR part 225 for medicated feeds, or 21 CFR part 226 for Type A medicated articles;
8. A written commitment to label, distribute, and promote the new animal drug only in accordance with the Index entry;
9. The name and address of the contact person or permanent-resident U.S. agent;
10. Copies of the first two pages of each literature article considered by the qualified expert panel; and
11. A draft Freedom of Information summary which includes the following information:
    - A general information section that contains the name and address of the requestor and a description of the drug, route of administration, indications, and recommended dosage.

- A list of the names and affiliations of the members of the qualified expert panel, not including their addresses or other contact information.
- A summary of the findings of the qualified expert panel concerning the target animal safety and effectiveness of the drug.
- Citations of all publicly-available literature considered by the qualified expert panel.
- For an early non-food life stage of a food-producing minor species animal, a human food safety summary.

If you have any questions, please contact me at *Insert Phone Number(s).*

Insert Signature Block

X enclosures

Please note: *the letter should be addressed to the Director, Office of Minor Use & Minor Species Animal Drug Development, HFV-50, Center for Veterinary Medicine, 7500 Standish Place, Rockville, Maryland, 20855. However, the package containing the letter should be mailed to the FDA/CVM Document Control Unit, HFV-199, 7500 Standish Place, Rockville, Maryland 20855.*

Appendix 4: Sample Report
Indexed Product Adverse Drug Experience Report

<table>
<tr><th colspan="6">INDEXED PRODUCT ADVERSE DRUG EXPERIENCE REPORT</th></tr>
<tr><td colspan="3" rowspan="3">1. Report Source and Address (Mfr./Distr.)</td><td colspan="2">2a. Date Report Received</td><td>3a. Type of Report
□ 3 Day □ 15 Day
□ Periodic</td></tr>
<tr><td colspan="2">2b. Date Sent to FDA</td><td rowspan="2">3b. □ Initial
□ Follow Up Report
Of (Give Date)</td></tr>
<tr><td colspan="2">2c. Number of Days
Between 2a. and 2b.</td></tr>
<tr><td colspan="3">4. Name, Address, and Phone Number of Attending Veterinarian (In confidence)</td><td colspan="3">5. Name or Case Identification of Owner (In confidence)</td></tr>
<tr><td colspan="3" rowspan="2">6. Trade Name and Generic Name of Active Ingredients (include dosage form and strength – Ex. tab, 500 mg)</td><td colspan="3">7a. Name of Manufacturer</td></tr>
<tr><td colspan="3">b. MIF Number</td></tr>
<tr><td colspan="2">8. Lot Number(s)</td><td colspan="2">9. Dosage Administration and Route</td><td colspan="2">10. Date(s) of Administration</td></tr>
<tr><td colspan="3">11. Reason for Use of Drug</td><td colspan="3">12. Drug Administered By
□ Veterinarian, Staff
□ Owner, Other</td></tr>
<tr><td colspan="3">13. Number of Animals in this Incident</td><td colspan="3">14. Reacting Animals</td></tr>
<tr><td>a. Treated with Drug</td><td>b. Reacted</td><td>c. Died</td><td colspan="2">a. Species</td><td>b. Breed</td></tr>
<tr><td colspan="3" rowspan="2">15. Concurrent Medical Problems</td><td>c. Age</td><td>d. Weight</td><td>e. Sex
□ Female □ Pregnant
□ Male □ Neutered</td></tr>
<tr><td colspan="3">16. Overall State of Health at Time of Reaction
□ Good □ Fair □ Poor □ Critical</td><td colspan="2">17. Did new illness develop or did initial diagnosis change after the drug was administered?
□ No □ Yes (Explain)</td></tr>
<tr><td colspan="6">18. Concurrent Drugs Administered</td></tr>
<tr><td colspan="2">Name of Drug</td><td>Route</td><td colspan="2">Dosage Regimen</td><td>Date(s) of Administration</td></tr>
<tr><td colspan="2"></td><td></td><td colspan="2"></td><td></td></tr>
</table>

19. DESCRIBE SUSPECTED ADVERSE REACTION: INCLUDE ALL SIGNS, RESULTS OF PERTINENT LABORATORY TESTS, NECROPSY RESULTS, POSSIBLE CONTRIBUTING FACTORS, ETC. ALSO, INCLUDE IN THIS SECTION PRODUCT EFFECTIVENESS AND PRODUCT DEFECTS SUCH AS CRACKED TABLETS, CLOUDY SOLUTIONS, ETC.		
20A. ATTENDING VETERINARIAN'S LEVEL OF SUSPICION THAT DRUG CAUSED REACTION □ HIGH □ MEDIUM □ LOW □ NO ATTENDING VET		20B. WAS THERE EXTRA LABEL USE (ELU) INVOLVED? □ NO □ YES (EXPLAIN)
21. LENGTH OF TIME BETWEEN LAST ADMINISTRATION OF THE DRUG AND ONSET OF REACTION	22. DATE OF ONSET (MONTH/DAY/YEAR)	23. DURATION OF REACTION (HOURS, DAYS, ETC.)
24. WAS THE ADVERSE REACTION TREATED? □ NO □ YES (DESCRIBE TREATMENT)		25. OUTCOME OF REACTION TO DATE □ DIED (GIVE DATE) □ REMAINS UNDER TREATMENT □ ALIVE WITH SEQUELAE □ RECOVERED □ UNKNOWN
26. WHEN THE REACTION APPEARED, TREATMENT WITH THE DRUG □ HAD ALREADY BEEN COMPLETED □ DISCONTINUED DUE TO THE REACTION □ DISCONTINUED, REPLACED WITH ANOTHER DRUG □ DISCONTINUED, REINTRODUCED LATER □ OTHER (EXPLAIN)	**AND THE REACTION**	□ CONTINUED □ STOPPED □ RECURRED □ OTHER (EXPLAIN)
27. HAD ANIMAL(S) BEEN PREVIOUSLY EXPOSED TO THIS DRUG? □ NO □ YES □ UNKNOWN		
28. DID ANIMAL(S) PREVIOUSLY REACT TO THIS DRUG? □ NO □ YES □ UNKNOWN		
29. HAD ANIMAL(S) PREVIOUSLY REACTED TO OTHER DRUGS? □ NO □ YES □ UNKNOWN		
HAS THE ATTENDING VETERINARIAN SEEN SIMILAR REACTIONS TO THIS DRUG IN OTHER ANIMALS? □ NO □ YES (IF YES, SUMMARIZE)		
NAME AND TITLE OF INDIVIDUAL RESPONSIBLE FOR ACCURACY OF REPORTED INFORMATION (TYPE OR PRINT)		SIGNATURE OF INDIVIDUAL RESPONSIBLE FOR ACCURACY OF REPORTED INFORMATION

Appendix 5: Sample Report
Annual Indexed Drug Experience Report

Annual Indexed Drug Experience Report			
1. Name of Holder		2. MIF Number	
3. Drug Name		4. Chemical Name	
5. Date Report Submitted		6. Reporting Period From: To:	
7. Quantity of Drug Marketed During Reporting Period (*See information on next page*)			
8. Adverse Drug Experiences (*See information on next page*)			
(a) Total Number of Reports	(b) Number of Product Defects	(c) Number of Complaints Affecting Animals	(d) Number of Animals Reacted
9. Have there been any changes to the labeling during the reporting period? Yes ☐ No ☐ (If yes, please describe the changes and attach a copy of the current labeling.)			
10. Have there been any changes to the manufacturing process for the drug during the reporting period? Yes ☐ No ☐ (If yes, please attach a summary of the changes.)			
11. Were there any nonclinical laboratory studies conducted and/or clinical data collected during the reporting period? Yes ☐ No ☐ (If yes, please attach a summary of the studies and/or clinical data.)			
12. Is there any other information pertinent to the safety and effectiveness of the drug to report? Yes ☐ No ☐ (If yes, please attach on a separate sheet.)			

Information to Submit for an Annual Indexed Drug Experience Report

See 21 CFR 516.165 for more information on required records and reports for indexed drugs.

7. Report the quantity marketed in units of highest concentration and the largest marketing package size. In the case of a dosage form product, e.g., tablets which are formulated on body weight range basis, give the quantity marketed of specific strength and package size separately without converting into highest concentration and the largest marketing package size unit.

8. An adverse drug experience is any adverse event associated with the use of an indexed drug, whether or not considered to be drug related. An adverse drug experience includes, but is not limited to:

   (1) An adverse event occurring in animals in the course of the use of an indexed drug product by a veterinarian or other animal owner or caretaker.
   (2) Failure of an indexed drug to produce its expected pharmacological or clinical effect (lack of expected effectiveness).
   (3) An adverse event occurring in humans from exposure during manufacture, testing, handling, or use of an indexed drug.

8(a). Enter total number of complaints being reported. Each complaint may involve one or more adverse drug reactions. A complaint is defined as a report involving one situation or incident and may involve one or more animals.

8(d). Enter total number of animals experiencing reactions involved in item 8(c).

8(a)-(d). Enter total numbers for the reporting period; including any adverse drug experiences previously reported through a Three-Day Indexed Drug Field Alert Report or a Fifteen-Day Indexed Drug Alert Report. If there are other adverse drug experiences that have not been previously reported, please provide a description of the event(s) on a separate sheet.