

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 20, 25, 201, 202, 207, 225, 226, 500, 510, 511, 515, 516, 558,  
and 589

[Docket No. 2006N-0067]

RIN 0910-AF67

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

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Proposed rule.

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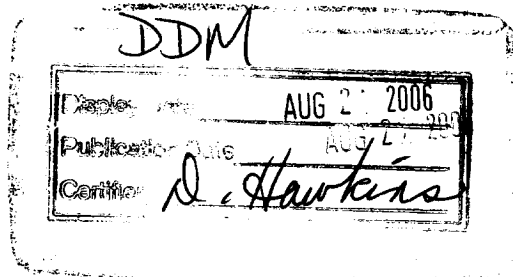
**SUMMARY:** The Minor Use and Minor Species Animal Health Act of 2004 (MUMS act) amended the Federal Food, Drug, and Cosmetic Act (the act) to authorize the U.S. Food and Drug Administration (FDA, the agency) to establish new regulatory procedures that provide incentives intended to make more drugs legally available to veterinarians and animal owners for the treatment of minor animal species and uncommon diseases in major animal species. At this time, FDA is issuing proposed regulations to implement section 572 of the act entitled "Index of Legally Marketed Unapproved New Animal Drugs for Minor Species." These regulations propose administrative procedures and criteria for index listing a new animal drug for use in a minor species. Such indexing provides a basis for legally marketing an unapproved new animal drug intended for use in a minor species.

**DATES:** Submit written or electronic comments on this document by [insert date 90 days after date of publication in the **Federal Register**]. Interested persons

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are requested to submit comments on the information collection provisions by [insert date 30 days after date of publication in the **Federal Register**].

**ADDRESSES:** You may submit comments, identified by [Docket No. 2006N-0067 and/RIN number 0910-AF67], by any of the following methods:

*Electronic Submissions*

Submit electronic comments in the following ways:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments.
- Agency Web site: <http://www.fda.gov/dockets/ecomments>. Follow the instructions for submitting comments on the agency Web site.

*Written Submissions*

Submit written submissions in the following ways:

- FAX: 301-827-6870.
- Mail/Hand delivery/Courier [For paper, disk, or CD-ROM submissions]:  
Division of Dockets Management (HFA-305), Food and Drug Administration,  
5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

To ensure more timely processing of comments, FDA is no longer accepting comments submitted to the agency by e-mail. FDA encourages you to continue to submit electronic comments by using the Federal eRulemaking Portal or the agency Web site, as described in the *Electronic Submissions* portion of this paragraph.

*Instructions:* All submissions received must include the agency name and Docket No(s). and Regulatory Information Number (RIN) for this rulemaking. All comments received may be posted without change to <http://www.fda.gov/ohrms/dockets/default.htm>, including any personal information provided. For detailed instructions on submitting comments and additional information on

the rulemaking process, see the "Comments" heading of the **SUPPLEMENTARY INFORMATION** section of this document.

*Docket:* For access to the docket to read background documents or comments received, go to <http://www.fda.gov/ohrms/dockets/default.htm> and insert the docket number(s), found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

To ensure that comments on the information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, FAX: 202-395-6974.

**FOR FURTHER INFORMATION CONTACT:** Andrew Beaulieu, Center for Veterinary Medicine (HFV-50), Food and Drug Administration, 7519 Standish Pl., Rockville, MD 20855, 240-276-9090, e-mail: [Andrew.Beaulieu@fda.hhs.gov](mailto:Andrew.Beaulieu@fda.hhs.gov).

**SUPPLEMENTARY INFORMATION:**

**I. Background**

In enacting the MUMS act (Pub. L. 108-282), Congress sought to encourage the development of animal drugs that are currently unavailable to minor species (species other than cattle, horses, swine, chickens, turkeys, dogs, and cats) in the United States or to major species afflicted with uncommon diseases or conditions (minor use). Congress recognized that the markets for drugs intended to treat these species, diseases, or conditions, are so small that there are often insufficient economic incentives to motivate sponsors to develop data to support approvals. Further, Congress recognized that some minor species populations are too small or their management systems too diverse to make it practical to conduct traditional studies to demonstrate safety and effectiveness of animal drugs for such uses. As a result of these limitations,

sponsors have generally not been willing or able to collect data to support legal marketing of drugs for these species, diseases, or conditions. Consequently, Congress enacted the MUMS act, which amended the Federal Food, Drug, and Cosmetic Act to provide incentives to develop new animal drugs for minor species and minor use, while still ensuring appropriate safeguards for animal and human health.

The major incentives of the MUMS act include the following:

(1) Designation, established by section 573 of the act (21 U.S.C. 360ccc-2), which provides for eligibility for grants and contracts to defray the costs of qualified safety and effectiveness testing expenses and manufacturing expenses incurred in the development of designated new animal drugs. Designation also provides for eligibility for a 7-year period of exclusive marketing rights to enable sponsors to recover costs of drug development without competition. FDA proposed regulations to implement the designation provision of the act on September 27, 2005 (70 FR 56394) (the designation proposed rule).

(2) Conditional approval, established by section 571 of the act (21 U.S.C. 360ccc), which provides for animal drug marketing after all safety and manufacturing components of a new animal drug approval have met the standards of section 512 of the act (21 U.S.C. 360b). For the effectiveness component, a reasonable expectation of effectiveness must be established, after which sponsors have up to 5 years to complete the demonstration of effectiveness by the standards of section 512 of the act and achieve a full approval. Regulations to implement the conditional approval provision will be proposed in the future.

(3) Indexing, established under section 572 of the act (21 U.S.C. 360ccc-1), which provides for the legal marketing of unapproved new animal drugs intended for use in a minor species through an integrated process of agency and expert panel review.

At this time, FDA is issuing proposed regulations to implement the indexing provisions of the MUMS act. These regulations propose procedures and criteria for index listing a new animal drug for use in a minor species. They describe a process whereby the agency makes a determination regarding the following: (1) The eligibility of a new animal drug, (2) the selection of a qualified expert panel, and (3) the findings of the qualified expert panel.

## **II. Proposed Regulations**

### *A. Definitions (proposed § 516.115).*

Most of the proposed definitions are straightforward. The proposed definition of “qualified expert panel” is drawn from the statutory definition, given in section 572(d)(3) of the act. The proposed definition of “transgenic animal” comes from the statutory definition, given in section 571(j) of the act (21 U.S.C. 360ccc). The proposed definition of “intended use” is identical to one proposed with respect to the designation proposed rule of September 27, 2005 (70 FR 56394). The designation proposed rule also included definitions for the phrases “same intended use,” “same drug,” and “same dosage form” that would be applicable to all subparts of part 516, including the indexing regulations.

### *B. Permanent-resident U.S. agent for a foreign requestor (proposed § 516.119).*

The proposed rule would require a foreign requestor or holder to name a permanent-resident U.S. agent so that the agency may ensure that

notifications of decisions regarding indexing and all other communications with the requestor or holder are legally and effectively made.

*C. Meetings (proposed § 516.121)*

The act provides that any person intending to file a request for eligibility or a request for addition to the index may have an opportunity to meet with the agency to discuss the requirements for indexing a new animal drug.

*D. Informal conferences regarding agency administrative actions (proposed § 516.123)*

The act also provides that a requestor or holder be offered an informal conference in association with an agency decision to deny a request for a determination of eligibility to index, to deny a request for index listing or to remove an index listing. Proposed § 516.123 establishes the nature of and the procedures for requesting and conducting such conferences. FDA would give notice of the grounds for the initial decision and provide an opportunity to respond to that decision. As proposed, the conference's presiding officer would not have significantly participated in the initial decision, would prepare a written summary of the informal conference to share with the participants, and would issue a written report describing the basis for his or her findings. The proposed regulation also provides for an informal conference associated with a decision to terminate an investigational exemption for a new animal drug proposed for indexing or a decision not to affirm an expert panel because it does not meet the selection criteria of § 516.141. In the case of conferences associated with adverse agency decisions, the proposed regulation establishes that decisions to deny, remove, terminate, or not affirm will be made by the Director, Office of Minor Use and Minor Species Animal Drug Development (OMUMS) and a subsequent conference, if requested, will be conducted by the

Director, Center for Veterinary Medicine or his designee, other than the Director, OMUMS. These procedures were adapted from the process for holding regulatory hearings before the agency under 21 CFR part 16.

*E. Investigational use of new animal drugs to support indexing (proposed § 516.125).*

As required by section 512(a)(1) of the act, a new animal drug may not be legally marketed unless it is the subject of an approved New Animal Drug Application (NADA), the subject of a conditionally approved NADA, or on FDA's list of legally marketed unapproved new animal drugs. The act contains two exemptions for drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs. The first, in section 512(j) of the act, applies to new animal drugs generally, including animal feeds bearing or containing new animal drugs. FDA's regulations implementing this investigational use exemption are at part 511 (21 CFR part 511). The second, in section 572(g) of the act, is parallel to the first exemption but is for the purposes of indexing and applies only to minor species new animal drugs, including animal feeds bearing or containing such new animal drugs. Note that the coverage of these exemptions overlaps and, therefore, in some circumstances an investigational use might qualify for an exemption under either section 512(j) of the act or section 572(g) of the act.

Proposed § 516.125 would implement section 572(g) of the act. It states that certain investigational uses, although they involve a minor species new animal drug, are nonetheless subject to part 511. Such uses include investigations to demonstrate safety with respect to individuals exposed to the new animal drug through its manufacture and use under section 572(c)(1)(F)

of the act, to conduct an environmental assessment under section 572(c)(1)(E) of the act, or to obtain approval of a new animal drug application or abbreviated new animal drug application under section 512(b) of the act. These investigational uses would be required to be conducted under part 511 because, whether these types of studies are conducted to support indexing or approval, the agency would evaluate the study results using the same standards. Thus, the agency believes it should apply the same substantive and procedural requirements for these investigational uses for minor species new animal drugs as it does for new animal drugs generally.

For other types of investigational uses, proposed § 516.125 establishes separate exemption regulations, although they are very similar to part 511. The agency believes the regulations should be similar because of the similarity of the purpose and the language of the two investigational use exemptions in the act. Proposed § 516.125 states that, with certain modifications, part 511 applies to minor species new animal drugs or animal feeds bearing or containing such new animal drugs intended for investigational use for all other purposes in support of a drug index listing (such as to demonstrate target animal safety and effectiveness). Among the proposed modifications is the need to specifically identify that the investigational use is in support of index listing, which would be done when labeling the drugs involved and when notifying the agency of the claimed investigational exemption. Another modification is that FDA would provide notice and an opportunity for an informal conference before terminating an investigational use exemption. While part 511 provides for notice and an opportunity for a hearing under 21 CFR part 16 concerning whether the exemption should be terminated, the administrative process in the proposed regulations reflects the fact that section 572 of the act provides



for an informal conference with respect to other agency decisions regarding indexing, such as removal of a new animal drug from the index. FDA does not believe it should have an administrative process for terminating an investigational use exemption relating to indexing that is different from the informal conference process for other decisions relating to indexing.

*F. Content and format of a request for determination of eligibility for indexing (proposed § 516.129).*

To be added to the index, a new animal drug must meet certain criteria. The act establishes what can be described as a two-part regulatory decision-making process for determining whether these criteria have been met. The first part in this regulatory process is FDA's determination of whether the new animal drug is eligible for indexing. This involves an evaluation of most of the indexing criteria, with the major exceptions being target animal safety and effectiveness. The second part includes the agency's determination of the suitability of the qualified expert panel and a review of whether the new animal drug meets the statutory criteria regarding target animal safety and effectiveness.

The determination of eligibility for indexing is initiated by a request to the agency that must be accompanied by sufficient information to permit the agency to make an informed decision regarding the request. The information proposed by the agency to determine eligibility for indexing, described in proposed § 516.129(c), is based on the requirements of 572(c)(1) of the act. The categories of information are described below:

1. Food safety

The act allows the indexing of new animal drugs that are intended for use in food-producing animals only in limited circumstances. The new animal

drug must be for use in an early, non-food life stage of a minor species; it must be intended for use only in a hatchery, tank, pond, or other similar contained man-made structure; and there must be sufficient information to demonstrate food safety in accordance with the standards of section 512(d) of the act (including, for an antimicrobial new animal drug, with respect to antimicrobial resistance).

When a new animal drug proposed for indexing is *not* intended for use in an early life stage of a food-producing minor species animal, the requestor must demonstrate that there is a reasonable certainty that the minor species or edible products from the minor species will not be consumed by humans or food-producing animals. For many minor species, this should be as straightforward as an affirmation that the species has never been traditionally consumed by humans and is not subject to being used in the feed of food-producing animals. A new animal drug intended for use in a wildlife species might be eligible for indexing if it could be demonstrated that there is a reasonable certainty that treated animals would not be subsequently harvested and consumed by humans or food-producing animals.

Under the proposed rule, FDA would rely on its existing regulations regarding the food safety standards of section 512(d) of the act, which are in part 514 (21 CFR part 514) at § 514.111, and be guided by relevant policies and guidance such as FDA's Guidance for Industry (GFI) #152.

## 2. Environmental assessments

Under the proposal, a request for eligibility would be required to contain either an environmental assessment or sufficient information to support a categorical exclusion from the requirement to prepare an environmental assessment. The proposal would rely on the process and the standards for

environmental assessments that are already defined in part 25 (21 CFR part 25). It would also amend part 25 to have categorical exclusions relating to indexing that parallel those relating to new animal drug approvals.

### 3. Occupational and user safety

As with new animal drug approvals, indexing includes a provision for a demonstration of safety to individuals exposed to the new animal drug during the drug's manufacture and use. FDA intends to rely on the same user safety standards for both drug approval and drug indexing.

### 4. Chemistry, manufacturing, and control information

The required chemistry, manufacturing, and control information, and the agency's review of that information, are much different for indexing than they are for approval.

A request for a determination of eligibility for a new animal drug for indexing must include "information regarding" the components and composition of the involved drug (section 572(c)(1)(C) of the act) and must also include "a description" of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the new animal drug (section 572(c)(1)(D) of the act) for the purpose of determining whether the requestor has an understanding of current Good Manufacturing Practices (cGMPs) and has established appropriate specifications for the manufacture and control of the new animal drug (section 572(c)(2)(C) of the act). In addition, before a new animal drug can be added to the index, the requestor must make a commitment that the indexed drug will be manufactured in compliance with cGMPs (section 572(d)(1)(F) of the act).

In contrast, an NADA must include a "full list" of the articles used as components of the drug and "a full statement" of the composition of the drug

(section 512(b)(1)(B), (C) of the act) as well as “a full description” of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the new animal drug (section 512(b)(1)(D) of the act). These statutory requirements, as implemented by regulation (21 CFR 514.1(b)(4), (5)), result in a highly detailed NADA submission which must contain sufficient information to permit FDA to determine the adequacy of the “full description” with respect to preserving the identity, strength, quality, and purity of the subject new animal drug (see section 512(d)(1)(C) of the act).

As previously stated, FDA believes that the submission of chemistry, manufacturing, and control information for a new animal drug proposed for indexing that would meet the relevant statutory standard would consist of a comprehensive summary of the manufacturing process that is sufficient to permit a determination that the requestor understands cGMPs and has established appropriate specifications in accordance with that understanding. FDA believes that the “full description” and underlying confirmatory information that are required in an NADA would not be necessary in a request for determination of eligibility for indexing.

## 5. Other Information

Proposed 21 CFR 516.129 also requires that a request for determination of eligibility contain the following: (1) Identification of the minor species or groups of minor species for which indexing is sought; (2) a statement of the intended use(s) in those species; (3) a statement of the conditions of use, such as dosage, route of administration, warnings, contraindications or other significant limitations associated with the intended use(s); (4) a brief discussion of the need for the drug for the intended use(s); and (5) an estimate of the anticipated annual distribution after indexing.

Additionally, the regulation provides that a single request for eligibility may involve only one drug (or combination of drugs) in one dosage form, may involve multiple intended uses or multiple minor species, may not involve a new animal drug that is contained in or a product of a transgenic animal, and may not involve the same drug in the same dosage form for the same intended use as a new animal drug that is already approved or conditionally approved.

*G. Granting and denying requests for a determination of eligibility and notification thereof (proposed § 516.133, § 516.135, and § 516.137).*

FDA will deny a request for determination of eligibility if a requestor fails to submit information required by section 572(c)(1) of the act, or the submitted information, evaluated together with other information available to the agency, is insufficient to support a decision to grant a request in accordance with section 572(c)(2) of the act.

The new animal drug that is the subject of the request must be sufficiently characterized to enable the agency to determine whether the same drug in the same dosage form for the same intended use is already approved or conditionally approved. The proposed designation rule contains a definition of sameness regarding these three elements that would also apply to indexing (see proposed § 516.3 published in the **Federal Register** of September 27, 2005 (70 FR 56394)).

FDA believes that the estimate of the quantity of the indexed drug likely to be distributed on an annual basis following indexing is primarily required because of concern over extralabel use of indexed drugs, which is statutorily prohibited. The anticipated quantity to be distributed for the intended purpose(s) can serve as a baseline against which actual distribution can be

measured. Significant differences between expected and actual distribution may indicate that an indexed drug is being used for other than its intended purposes. An estimation of the quantity of drug likely to be distributed may also inform decisions associated with the extent of environmental or user exposure following indexing.

As previously noted, a new animal drug which is contained in or is the product of a transgenic animal may not be indexed. A transgenic animal is defined, in section 571(j) of the act, as an animal whose genome contains a nucleotide sequence that has been intentionally modified in vitro, and the progeny of such an animal; provided that the term "transgenic animal" does not include an animal of which the nucleotide sequence of the genome has been modified solely by selective breeding.

Under the proposal, FDA cannot determine a drug to be eligible for indexing if the information submitted in support of the request evaluated together with other information available to the agency is insufficient to do the following: (1) Demonstrate food safety in an early, non-food life stage of a food-producing minor species animal or demonstrate that there is a reasonable certainty that treated animals will not be consumed by humans or food-producing animals, (2) determine that the requestor has established appropriate specifications for the manufacture and control of the new animal drug, (3) demonstrate that the requestor has an understanding of current good manufacturing practices, or (4) determine that the new animal drug is safe with respect to individuals exposed to the new animal drug during manufacture or use; or the request fails to include an adequate environmental assessment or sufficient information to support a categorical exclusion from the requirement to prepare an environmental assessment.

In addition, under the proposal a request for a determination of eligibility for indexing may be denied if it contains any untrue statement of a material fact or omits material information.

Within 90 days after the submission of a request for a determination of eligibility for a non food-producing animal, or 180 days for a request for an early, non-food life stage of a food-producing animal, FDA must grant or deny the request and notify the requestor of its decision in writing. If FDA denies the request, the agency will provide due notice and an opportunity for an informal conference regarding its decision. A decision of FDA to deny a request for determination of eligibility for indexing following an informal conference would constitute the final agency action subject to judicial review.

*H. Qualified expert panels (proposed § 516.141).*

Once a requestor has received a letter granting eligibility for indexing, as the first step in the process of requesting an index listing, it can propose a qualified expert panel. The panel, which operates external to FDA, plays a central role in the indexing process—evaluating target animal safety and effectiveness information and making a recommendation to FDA based on its evaluation. Section 572(d) of the act requires the agency to “define the criteria for selection of a qualified expert panel and the procedures for the operation of the panel.” The same section states that the panel is not subject to the Federal Advisory Committee Act, also known as FACA. Section 516.141 of the proposed implementing regulations describes the process for selecting the qualified expert panel and describes how the panel operates. It does this by stating the responsibilities of each of the parties involved—the requestor, FDA, the panel members, and the panel leader.

Because of the diverse nature of the products that are subject to indexing and anticipated differences in the availability and accessibility of experts qualified to review different product classes, the proposed rule does not specify the day-to-day operations of a qualified expert panel other than to require that the activities of the panel be conducted in accordance with generally accepted professional and ethical business practices and that one member of the panel be identified to serve as the "leader" of the review process. The leader would serve as the principal spokesperson for the panel and be responsible for submitting the panel's final written report to the requestor and maintaining records of the final report. In addition, the agency plans to issue guidance documents regarding other aspects of the operation of expert panels and the preparation of written reports.

In developing the selection criteria for the qualified expert panel, FDA adapted some aspects of the agency's implementation of section 523 of the act (21 U.S.C. 360m). That provision deals with FDA accreditation of persons in the private sector to conduct the initial pre-market review for certain medical devices. FDA also considered its use of advisory committees that review information and make recommendations to FDA on various technical and scientific issues relating to product approval. In addition, FDA tried to minimize the burden on the potential members to help ensure that qualified individuals will be willing to participate while still establishing adequate controls to help ensure that FDA obtains objective, high quality evaluations and recommendations.

To maintain the integrity of the review process, one proposed selection criterion is that a qualified expert panel member must not have a conflict of interest or the appearance of a conflict of interest, unless FDA makes a



determination to allow participation notwithstanding an otherwise disqualifying financial interest. The proposed rule describes the factors that are, and are not, relevant to determining whether there is a conflict of interest or the appearance of a conflict of interest and identifies the information needed from potential panel members to support this determination by the agency. Proposed § 516.141(e)(7) requires qualified expert panel members to immediately notify the requestor and FDA of any change in conflict of interest status. For purposes of this regulation, the agency believes that this generally requires a panelist to report changes in his conflict of interest status within 30 days.

In selecting members for the qualified expert panel, the person requesting the index listing would be required to ensure that the members have the requisite scientific training and experience to evaluate the target animal safety and effectiveness of the new animal drug at issue for the proposed intended use. The group of identified experts would also be required to represent an adequate range of expertise to fully evaluate the product.

After identifying potential panel members, the requestor would be required to provide their names and addresses to FDA, along with sufficient information about each proposed member for FDA to determine whether the panel meets the selection criteria other than with respect to potential conflicts of interest. Each proposed panel member would provide information regarding potential conflicts of interest directly to the agency. If the agency determines that the qualified expert panel does not meet the selection criteria, it will provide information to the requestor so that a suitable panel can be proposed. For example, FDA may decline some candidates and request replacements or request that the panel include additional members to provide needed expertise.

If the requestor disagrees with FDA's determination regarding the panel, under the proposal it may request review through an informal conference.

The work of the expert panel centers around its primary task, which is to prepare a written report that describes the panel's evaluation of all available target animal safety and effectiveness information relevant to the proposed use of the new animal drug and the panel's conclusions based on its evaluation. In preparing the written report, panel members would be required to review all relevant information provided by the requestor and should also consider any other relevant information otherwise known by panel members, including anecdotal information. Panel members would be required to participate in the preparation of the written report. Members could be paid a reasonable fee to serve on expert panels by the requestor.

*I. Written report (proposed § 516.143).*

The qualified expert panel's written report must meet the requirements of section 572(d)(2) of the act. Under proposed § 516.143, which would implement this provision, the report must describe the panel's evaluation of all available target animal safety and effectiveness information relevant to the proposed use of the new animal drug; provide citations of all literature reviewed and summaries of unpublished information considered; and state the panel's opinion regarding whether the benefits of using the new animal drug for the proposed use in a minor species outweigh its risks 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. The purpose of these requirements is to provide sufficient information to permit the agency to assess the quality and quantity of the information relating to target animal safety and effectiveness of the new animal drug assessed by

the panel. Therefore, the panel's evaluation should be such that FDA can understand the basis for the panel's conclusion regarding the drug's benefits and risks. If the expert panel concludes that the benefits of using the drug outweigh its risks, it would also be required to provide as part of the report either draft labeling, which includes all conditions of use deemed necessary by the expert panel to assure that the benefits of the drug will outweigh its risks, or narrative information on the basis of which such labeling can be drafted by the requestor. All panel members would be required to sign the report or otherwise approve it in writing.

*J. Content and format of a request for addition to the index (proposed § 516.145).*

As noted previously, the second part of the indexing regulatory process involves FDA's review of whether the new animal drug meets the statutory criteria regarding target animal safety and effectiveness information. FDA's review is based on the qualified expert panel's written report and recommendation. The agency's review begins with the requestor's submission asking for addition of the new animal drug to the index. This submission must contain the information required by section 572(d)(1) of the act. FDA's decision to grant or deny the request for indexing is governed by section 572(d)(4) of the act. Therefore, the request for addition to the index needs to contain sufficient information to permit FDA to grant the request. The sections of the proposed rule that implement these statutory provisions are sections 516.145 and 516.149, respectively.

*K. Refusal to file and review a request for addition to the index (proposed § 516.147).*

The agency proposes that if a request for indexing fails to contain information required by § 516.145, FDA will not file or review it and will so notify the requestor within 30 days of receiving the request.

*L. Granting or denying a request for addition to the index and notification thereof (proposed § 516.149, § 516.151, and § 516.153).*

FDA must deny a request for indexing if the same drug in the same dosage form for the same intended use is approved or conditionally approved. While this is also a basis for denying eligibility for indexing, it is possible that a new animal drug may be approved or conditionally approved between the time that a determination for eligibility is made and the request for indexing is submitted, thus preventing the indexing of a new animal drug previously determined to be eligible.

It is also possible that new scientific information may arise between the time of a determination of eligibility and submission of a request for indexing. Section 572(d)(4) of the act (by reference to section 572(a) of the act) and proposed § 516.151 require the agency in reviewing a request for index listing to evaluate any new information together with the information available at the time of a determination of eligibility to determine whether the new animal drug is still eligible for indexing.

If a request for indexing fails to contain, or appropriately reference, information required by the statute, as implemented by proposed § 516.145, the agency would be required to deny the request.

In general, FDA intends to rely heavily on the recommendations of the qualified expert panel regarding target animal safety and effectiveness,

including the necessary conditions of use. However, the written report of a qualified expert panel may not be sufficiently clear or complete with respect to the basis for a panel recommendation to index a new animal drug to permit FDA to make an informed decision regarding whether it agrees with the recommendation. In this case, FDA would either deny the request for indexing or, under proposed § 516.145(c), require that the requestor submit the information provided to the panel. It is also possible that, in some cases, the written report of an expert panel may be sufficiently clear and complete for the agency to make a decision regarding the panel recommendations, but the agency may disagree in whole or in part with the recommendations. Such disagreement may be based on the written report itself or the report along with additional information available to the agency. In such a case, FDA would deny the request. If FDA denies a request for addition to the index, the requestor could submit another request, which contains information to overcome the agency's grounds for denial.

One of the grounds for denying a request for addition to the index is that the qualified expert panel failed to meet one or more of the selection criteria. Proposed § 516.141 would require panel members to submit any new information regarding conflicts of interest to the agency so that FDA can determine whether a disqualifying conflict has arisen since the agency's initial review.

Under the proposal, and consistent with FDA's regulations governing new animal drug applications, FDA may also deny a request for addition to the index if it contains any untrue statement of a material fact or omits material information.

Within 180 days after the filing of a request for addition of a new animal drug to the index, FDA will grant or deny the request, and notify the person requesting indexing of FDA's decision in writing. If FDA denies the request for indexing of a new animal drug, the agency will provide due notice and an opportunity for an informal conference. A decision by FDA to deny a request to index a new animal drug following an informal conference will constitute final agency action subject to judicial review.

*M. Publication of the index and content of an index listing (proposed § 516.157).*

FDA proposes to meet the requirement of section 572(e)(2) of the act by maintaining and updating, at least annually, a publicly available list of indexed drugs. Each index listing would contain the following: (1) The name and address of the person who holds the index listing; (2) the name of the new animal drug and the intended use and conditions of use for which it is indexed, (3) product labeling, and (4) conditions and any limitations that the agency deems necessary regarding the use of the new animal drug.

*N. Modifications to indexed drugs (proposed § 516.161).*

As with approved new animal drugs, and as provided for by section 572(e)(3) of the act, there will almost certainly be a need to change the conditions under which a new animal drug is indexed or other aspects of an indexed drug at some point after indexing. The proposed regulations for making such changes are based on those governing new animal drug applications, although the proposed regulations are generally less burdensome than the regulatory requirements of the corresponding section of 21 CFR part 514.

Proposed § 516.161 provides for three classes of changes to indexed drugs.

The first class of changes involves the following: (1) The addition to labeling or prescription drug advertising of additional warning, contraindication, side effect, or cautionary information, (2) the deletion from labeling or prescription drug advertising of false, misleading, or unsupported indications for use or claims of effectiveness, or (3) changes in manufacturing methods or controls required to correct product or manufacturing defects that may result in serious adverse drug events. Changes of this nature should be made as soon as possible and a request for modification of an index listing containing information describing the need for the change should be concurrently submitted to the agency.

The second class of changes involves the following: (1) Addition of an intended use, (2) addition of a species, (3) addition or alteration of an active ingredient, (4) alteration of the concentration of an active ingredient, (5) alteration of the dose or dosage regimen, or (6) alteration of prescription or over-the-counter status. Changes of this nature can be made only after a request to make such a change has been granted by FDA. Each such change must go through the same review process as the original index listing. Therefore, the initial submission to FDA relating to such a change should be a request for a determination of eligibility for indexing that relates specifically to the proposed change. However, while the process for modifications to index listings of this kind follows the same process as a new index listing, much of the work to support the initial listing might also support the change to the listing and so would not have to be duplicated. Likewise, the panel that reviewed the original request for listing would likely be acceptable to review the proposed change as well. The agency notes, however, that the nature of the change or new information about, for example, the product's safety or

effectiveness, may mean that previous work would no longer be adequate to support the change.

The third class of changes involves any change to the conditions established in labeling or otherwise described in the request for determination of eligibility or request for indexing at the time a new animal drug was indexed other than those noted above. Information describing such changes would be required to be submitted as part of the annual indexed drug experience report. These changes include changes to the formulation of the product or to the manufacturing methods or controls other than those to correct defects that may cause serious adverse drug events. Changes to the formulation or manufacturing process would be required to be reported at the same level of detail as the level of detail at which the formulation or manufacturing process were initially described in the request for determination of eligibility for indexing.

The proposed provisions under § 516.161 would apply only to modifications to the indexed drug. Regardless of which class of changes is requested, these provisions would not apply to changes that would cause an indexed drug to be a different drug (or different combination of drugs) or a different dosage form. In the case of such a submission, the agency would deny the request for modification and notify the holder that a new index listing is required for the new drug or dosage form. The designation proposed rule (September 27, 2005, 70 FR 56394) contains proposed definitions for “same drug” and “same dosage form.” The holder could then initiate the new listing by submitting a request for eligibility for the new drug or dosage form.



*O. Change in ownership of an index file (proposed § 516.163).*

The agency proposes that, in order to meet the requirement of section 572(e)(1)(A) of the act, the owner of an index file supporting an index listing may transfer ownership of the file provided that the agency is appropriately notified of this. The agency would then update the index listing accordingly.

*P. Records and reports (proposed § 516.165).*

Section 572(i) of the act requires the maintenance of records and the submission of reports sufficient to permit a determination of whether an indexed drug should be removed from the index. The information FDA believes is necessary to make this determination is described in proposed § 516.165. This information would be similar in nature but less extensive than the information required with respect to approved new animal drugs. Most of the information required would be submitted annually, on, or within 60 days of, the anniversary date of the letter granting the request for indexing.

Under the proposed regulation, product or manufacturing defects that may result in serious adverse drug experiences must be reported to the appropriate FDA District Office or resident post within three working days of their discovery. Serious and unexpected adverse drug experiences must be reported to the Director, OMUMS within 15 working days of the index holder first receiving the information.

Distribution of an indexed drug by a distributor would be permissible provided that the holder of the index listing submits a special report at the time of initial distribution by the distributor containing the information required under proposed § 516.165. This includes a signed statement from the distributor that the indexed drug will be distributed and promoted only in accordance with the index listing.

The agency proposes that all other required information be submitted annually. This includes the following: The quantity of the drug distributed (domestically and for export), holder and distributor current package labeling with a summary of any changes in labeling since the previous annual report, a summary of changes in the manufacturing process (at the level of detail that the manufacturing process was described in the request for determination of eligibility) not already reported under proposed § 516.161, any pertinent safety or effectiveness information not previously reported, and any adverse drug experience information not previously reported.

*Q. Removal from the index (proposed § 516.167).*

Proposed § 516.167 provides for removal of a new animal drug from the index, after due notice to the holder of the index listing and an opportunity for an informal conference.

The proposed grounds for removal, which track those in the act, include that the same drug in the same dosage form for the same intended use has been approved or conditionally approved.

In accordance with section 572(f)(1) of the act, if FDA determines, subsequent to the indexing of a new animal drug, that the qualified expert panel failed to meet its applicable requirements, FDA would remove the drug from the index.

In light of the purpose of the MUMS act to increase the availability of legally marketed new animal drugs to treat minor species, the agency proposes to only partially remove an index listing if it believes that doing so would satisfactorily resolve a safety or effectiveness issue otherwise warranting complete removal of the drug from the index. For example, if an index listing provides for the use of a new animal drug in several minor species and new

information indicates that the benefits of using the drug in one of those minor species does not outweigh its risks to that species, the agency may remove only the use of the new animal drug in that minor species from the index listing.

In accordance with section 572(f)(2) of the act, the regulation proposes that FDA may immediately suspend a new animal drug from the index if it determines that there is a reasonable probability that the use of the drug would present a risk to the health of humans or other animals. The agency would subsequently offer the holder of the index listing an opportunity for an informal conference.

A decision by FDA to remove a new animal drug from the index following an informal conference would constitute final agency action subject to judicial review.

*R. Confidentiality of data and information in an index file (proposed § 516.171).*

This proposed regulation is based on § 514.11, which applies to new animal drug application files. It would apply to index files, which would encompass all data and information submitted to or incorporated by reference into the index file including requests for determination of eligibility for indexing, information supporting selection of expert panel members, requests for addition to the index, claimed investigational exemptions under proposed § 516.125, requests for modification to indexed drugs, reports submitted under proposed § 516.165, and master files.

### **III. Conforming Changes**

FDA is proposing conforming changes to certain applicable sections of the Code of Federal Regulations (CFR) that would add a reference to new animal

drugs that are index listed under section 572 of the act. The affected sections in title 21 of the CFR are:

§ 20.100 Applicability; cross-reference to other regulations.

§ 25.33 Animal drugs.

§ 201.105 Veterinary drugs.

§ 201.115 New drugs or new animal drugs.

§ 201.122 Drugs for processing, repacking, or manufacturing.

§ 202.1 Prescription-drug advertisements.

§ 207.21 Times for registration and drug listing.

§ 207.35 Notification of registrant; drug establishment registration number and drug listing number.

§ 225.1 Current good manufacturing practice.

§ 225.35 Use of work areas, equipment, and storage areas for other manufacturing and storage purpose.

§ 225.135 Work and storage areas.

§ 226.1 Current good manufacturing practice.

§ 500.25 Anthelmintic drugs for use in animals.

§ 500.26 Timed-release dosage form drugs.

§ 510.301 Records and reports concerning experience with animal feeds bearing or containing new animal drugs for which an approved medicated feed mill license application is in effect.

§ 510.305 Maintenance of copies of approved medicated feed mill licenses to manufacture animal feed bearing or containing new animal drugs.

§ 510.455 Requirements for free-choice medicated feeds.

§ 511.1 New animal drugs for investigational use exempt from section 512(a) of the act.

§ 515.10 Medicated feed mill license applications.

§ 515.21 Refusal to approve a medicated feed mill license application.

§ 558.3 Definitions and general considerations applicable to this part.

§ 558.5 Requirements for liquid medicated feed.

§ 558.6 Veterinary feed directive drugs.

§ 589.1000 Gentian violet.

In § 201.105, FDA is also proposing to remove a reference to certification requirements applicable to preparations of antibiotic drugs. FDA no longer certifies or recognizes certification of antibiotic drugs.

In addition, FDA is proposing to remove the last sentence in § 500.25(c) because it cites § 514.9 which no longer exists. Labeling revisions for animal feeds bearing or containing anthelmintic drugs are now subject to the same requirements under 21 CFR 500.25 as dosage form drugs. Medicated animal feeds covered by approved applications are subject to the provisions of § 514.8 (d) and (e). Medicated animal feeds covered by an index listing are subject to the provisions of 21 CFR 516.161(b)(1).

#### **IV. Legal Authority**

FDA's authority for issuing this proposed rule is provided by the MUMS act (21 U.S.C. 360ccc *et seq.*). When Congress passed the MUMS act, it directed FDA to publish implementing regulations (see 21 U.S.C. 360ccc note). In the context of the MUMS act, the statutory requirements of section 572 of the act, along with section 701(a) of the act (21 U.S.C. 371(a)) provide authority for this proposed rule. Section 701(a) authorizes the agency to issue regulations for the efficient enforcement of the act.

#### **V. Analysis of Economic Impacts**

FDA has examined the impacts of the proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act (Public Law 104–4). Executive Order 12866

directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; and distributive impacts and equity). The Regulatory Flexibility Act (5 U.S.C. 601–612) requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities.

FDA tentatively finds that the proposed rule does not constitute an economically significant regulatory action as defined in 3(f)(1) of Executive Order 12866. We base this on the following analysis that estimates annual costs ranging from about \$342,000 in the first year to about \$735,000 in the 10th year. Similarly, the administrative costs are unlikely to have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing “any rule that may result in an annual expenditure by State, local and tribal governments, in the aggregate, or by the private sector, of \$100 million (adjusted annually for inflation) in any one year.” The current threshold after adjustment for inflation is \$115 million, using the most current (2003) implicit price deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount. As such, no further analysis of anticipated costs and benefits is required by the Unfunded Mandates Reform Act.

*Summary*

The proposed rule is expected to result in about 30 requestors, each averaging about 2 requests for a determination of eligibility for indexing of individual animal drugs annually, submitting a total of 60 requests annually. We estimate that requestors for 20 of these products will create and convene expert panels to review the safety and efficacy data. Further, the recommendations of these panels are expected to lead to the addition of 20 animal drug index listings each year.

### *Benefit*

This rule intends to create administrative practices and procedures for index listing a new animal drug for use in a minor species, thereby providing the benefit of a legal basis for marketing an unapproved new animal drug intended for use in a minor species. The need for the rule arises from the existence of some minor species populations that are too small to support traditional drug approval studies. The countervailing risk of this rule is that sponsors of animal drugs that are marginally economically viable could use this system to avoid the traditional animal drug approval process. Under this proposed rule, however, the voluntary indexing of a new animal drug for use in a minor species would only be allowed when the same drug in the same dosage form for the same intended use is not already approved or conditionally approved, thereby reducing this risk.

### *Administrative Costs*

This section will describe and estimate the annual administrative costs by proposed provision for both producers of currently unapproved drugs that would request an index listing and FDA. First, we address the efforts required by requestors concerned with index listing. The estimates of the number of requestors, frequencies of responses, and hours per procedure for each of the

provisions of the proposed rule were determined by Center for Veterinary Medicine personnel.

We estimate that, on average, two foreign requestors of drug indexing would need to hire a permanent resident agent to represent them. We expect this to require about 1 hour of administrative time for a requestor's management employee in regulatory affairs. We estimate the loaded wage estimate at \$42.29 per hour (including a 30 percent increase for benefits) for regulatory affairs personnel.<sup>1</sup> This provision would cost the two requestors a total of about \$85. We expect that a resident agent would expend only about 6 hours of administrative effort per year per indexed drug. We estimate the wage rate of the resident agent at \$100 to \$150 per hour, and use the midpoint, \$125, for our calculations. Total annual costs for resident agents are estimated at \$1,500 (two agents times 6 hours times \$125 per hour) in the first year. In the 10th year this is expected to rise to about \$15,000 as two more resident agents each provide 6 more hours of administrative effort each additional year. Due to the uncertainty in the costs for resident agents, we request public comment and data on this issue.

Proposed § 516.121 provides for one or more meetings between requestors and FDA to discuss the requirements for indexing a new animal drug. We estimate that 30 requestors will each request, on average, 2 meetings annually, for a total of 60 meetings. Preparation and participation in these meetings is estimated at 4 hours each, for an annual total of 240 hours. Proposed § 516.123 concerns informal conferences regarding agency administrative actions. These would include conferences to discuss a request for determination of eligibility

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<sup>1</sup>2004 National Industry-Specific Occupational Employment and Wage Estimates, U.S. Department of Labor, Bureau of Labor Statistics ([http://www.bls.gov/oes/current/naics4\\_325400.htm](http://www.bls.gov/oes/current/naics4_325400.htm)); compliance officer wage rate for pharmaceutical and medicine manufacturing (NAICS 325400).



that has been denied, the removal of an expert panel member, a request for indexing that was denied or an indexed drug that was removed from the list. We estimate that about three requestors would request one conference with FDA annually for any of these reasons. We expect that each requestor would expend about 8 hours (24 hours total) to prepare for and attend each of these conferences. The combined efforts for preparation and participation in all conferences are estimated at 264 hours (240 plus 24). At the same loaded wage estimate of \$42.29 per hour, this provision is expected to cost about \$11,200 annually.

For proposed § 516.125, we estimate that two requestors would each annually submit three notices of claimed investigational exemptions for new animal drugs for index listing. We estimate that each submission would require about 20 hours for regulatory affairs personnel to prepare. At the loaded wage estimate of \$42.29 per hour, the total of 120 hours would cost about \$5,100.

We estimate that about 30 requestors would each average about 2 requests for determination of eligibility for indexing of individual animal drugs annually, totaling to 60 requests annually for proposed § 516.129. At the loaded wage estimate of \$42.29 per hour, and our estimate of 12 hours of preparation for each request, this provision would require about 720 hours equal to about \$30,400. Included in this estimate of 60 requests are any resubmitted requests that were previously denied.

Proposed § 516.141 would require the creation of a qualified expert panel to review all information, provided by any source, relevant to a determination of the target animal safety and effectiveness of the new animal drug. FDA would be required to approve the panel members before the panel formally convened. We estimate that requestors of 20 animal drugs, or about one-third

of the 60 animal drugs that annually are determined to be eligible for indexing, would create qualified expert panels to further study the safety and efficacy data. The creation of each panel by a requestor is estimated to take about 8 hours of effort by regulatory affairs personnel. At the same loaded wage estimate, these 160 hours would cost about \$6,800 annually.

Proposed § 516.143 describes how the expert panel would prepare a written report for FDA with its findings concerning the new animal drug under consideration for index listing. The review of the relevant information and preparation of the report by each panel would take an estimated 80 hours. This equates to 1,600 hours for 20 panels. The proposed rule allows for fees to be paid to panel members for their time. We estimated the average wage rate for panel members at \$100 to \$150/hr, and use the midpoint (\$125) in our calculations. At this wage, we estimate these activities to cost up to \$200,000 annually for the total industry, or \$10,000 per requestor for each animal drug under consideration. An additional 0.5 hours is estimated for recordkeeping of the final written report described in proposed § 516.143 by the panel leader. This would result in an additional \$400 in costs annually. We request comment and data on the range of hourly wage rates for qualified panel members.

We estimate that the formal request for addition to the index, provided for in proposed § 516.145, would require about 12 hours to prepare. This would result in another 240 hours of effort (20 requests times 12 hours) for regulatory affairs personnel. We project the compliance cost of this effort at \$10,200 annually.

We only expect to receive one request each for a modification to an indexed listed drug and a change in ownership of an index file annually

(provided for in proposed §§ 516.161 and 516.163), and estimate the preparation of each to require 4 and 2 hours, respectively. In total, these compliance efforts would cost about \$250 in the first year. Total modification requests and ownership change notifications are expected to increase by 1 each year so that 10 of each would be expected to be submitted in year 10. The cost of these provisions in year 10 is estimated at about \$2,500.

This proposed rule would require, in § 516.165, that records and reports be created, submitted and retained by the holder of the indexed drug. These records include a 3-day indexed drug field alert report, a 15-day indexed drug field alert report and an annual indexed drug experience report. We expect that the vast majority of compliance efforts will be associated with the annual indexed drug experience report. Because the number of expected requests that are granted for addition to the index is 20 per year (on average, 20 requestors with 1 request granted each), the number of reports to be created, submitted and stored is also estimated at 20 per year. We estimate the reports for each index listing would require 8 hours annually, totally about 160 hours for all 20 listings. At the loaded wage estimate of \$42.29 per hour, we estimate the first-year reporting costs at about \$6,800. These annual costs will increase by an additional \$6,800 each year as an additional 20 indexed drugs are added to the list. In year 10 we estimate the cost of this provision at about \$67,700. Further, we expect that the maintenance of these records (recordkeeping) would require an additional hour of administrative time for each indexed drug listing. These additional 20 hours would cost about \$850 at the same loaded wage estimate in the first year, and would also increase in succeeding years by an additional \$850 as additional indexed drugs are added to the list. We estimate the cost of this provision in year 10 at about \$8,500.

For those choosing to seek a MUMS index listing of an unapproved animal drug, total requestor compliance costs are expected to sum to about \$273,000 in the first year. These costs would be borne by 30 requestors at an average cost per requestor of about \$9,100 per indexed drug. Costs in succeeding years would be expected to increase slightly due to the annual reporting requirements for all indexed drugs resulting in year-10 costs of about \$358,000.

#### *Costs to Government*

The Government would also incur costs for this proposed rule. We expect that about 60 percent of a full-time equivalent employee at a GS-14 salary would be needed to handle the administrative work of the indexing of MUMS drugs in the first year. This would include all administrative efforts from responding to requests for presubmission meetings to making changes to approved indexed drugs. We estimate Government costs (including a 30 percent adjustment for benefits) of this provision at about \$69,000 in the first year. In year 10 we estimate that up to four full time equivalent employees (one GS-14 position, two GS-13 positions and one GS-11 position) would be needed to administer the program. Including a 30 percent adjustment for benefits, we estimate that the cost to Government in year 10 could increase to about \$378,000.

Total costs for this proposed rule would be the sum of private administrative and Government costs. Total costs are estimated to increase from \$342,000 in the first year up to \$735,000 in the 10th year.

#### *Regulatory Flexibility Analysis*

##### 1. Small Business Impacts

The Regulatory Flexibility Act requires agencies to prepare a regulatory flexibility analysis if a rule is expected to have a significant economic impact

on a substantial number of small entities. Although we believe it is unlikely that significant economic impacts would occur, the following constitutes the initial regulatory flexibility analysis.

One requirement of the Regulatory Flexibility Act is a succinct statement of any objectives of the rule. As stated previously in this analysis, with this rule the agency intends to create an administrative system, provided for by statute, that would allow for the legal marketing of unapproved animal drugs for intended uses in minor species in the U.S. that would otherwise not be economically viable under current market conditions.

The Regulatory Flexibility Act also requires a description of the small entities that would be affected by the rule, and an estimate of the number of small entities to which the rule would apply. The Small Business Administration (SBA) defines the criteria for small businesses using the North American Industrial Classification System (NAICS). For pharmaceutical preparation manufacturers (NAICS number 325412), SBA defines small businesses as those with less than 750 employees. Census data shows that 723 companies with 901 establishments represent this category.<sup>2</sup> While about two-thirds of the establishments would be considered small using the SBA criteria, the agency acknowledges that many requests for MUMS index listing would likely be received from multi-establishment companies that exceed the 750-employee limit on small businesses. Nonetheless, the average cost for a requestor that has two meetings with us, requests a determination of eligibility for indexing, creates and convenes a qualified panel of experts resulting in a written report, requests an addition to the index and keeps all necessary records, would be about \$12,600. This cost per request represents about 1.5

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<sup>2</sup>2002 Economic Census, U.S. Census Bureau, Manufacturing Industry Series, Pharmaceutical Preparation Manufacturing, Tables 3 and 4.

percent of the revenues of the smallest set of establishments (those with one to four employees), and less than 0.4 percent of revenues of all larger establishments. These costs would not represent a significant economic impact on these firms, especially in light of the fact that they incur these expenses in order to realize increased sales revenue from the indexing. The firms submitting requests for index listing are expected to already have the necessary administrative personnel with the skills required to prepare the requests and fulfill reporting requirements as identified above.

## 2. Analysis of Alternatives

The Regulatory Flexibility Act requires that the agency consider any alternatives to the proposed rule that would accomplish the objective while minimizing significant impacts of the rule. As stated previously, the agency believes that the proposed rule, due to the relatively small size of the costs, would not be likely to impose significant economic impacts on a substantial number of small businesses.

The statute that creates this system, Pub. L. 108-282, does not provide the agency a great deal of flexibility in the implementing regulations, such as in determining whether or not to use independent qualified expert panels to review the safety and efficacy data. We conclude that the proposed rule achieves the objective of increasing drug availability for minor species with minimal costs to industry while staying within the limits set by Pub. L. 108-282.

## VI. Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB), under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501-3520). A

description of these provisions is given below with an estimate of the annual reporting and recordkeeping burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

FDA invites comments on these topics: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility and clarity of the information to be collected; (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques and other forms of information technology.

*Title:* Index of Legally Marketed Unapproved New Animal Drugs for Minor Species 21 CFR Part 516

*Description:* The Minor Use and Minor Species Animal Health Act of 2004 (MUMS act) amended the Federal Food, Drug, and Cosmetic Act (the act) to authorize FDA to establish new regulatory procedures intended to make more medications legally available to veterinarians and animal owners for the treatment of minor animal species (species other than cattle, horses, swine, chickens, turkeys, dogs, and cats), as well as uncommon diseases in major animal species.

The MUMS act created three new sections to the act (section 571, 572, and 573), and this proposed rule is intended to implement section 572 of the act, which provides for an index of legally marketed unapproved new animal

drugs for minor species. Participation in any part of the MUMS program is optional so the associated paperwork only applies to those who choose to participate. The proposed rule specifies, among other things, the criteria and procedures for requesting eligibility for indexing and for requesting addition to the index as well as the annual reporting requirements for index holders.

Under the new subpart C of part 516, proposed § 516.119 provides requirements for naming a permanent-resident U.S. agent by foreign drug companies, and § 516.121 would provide for informational meetings with FDA. Section 516.123 provides proposed requirements for requesting informal conferences regarding agency administrative actions and proposed § 516.125 provides for investigational use of new animal drugs intended for indexing. Provisions for requesting a determination of eligibility for indexing can be found under proposed § 516.129 and provisions for subsequent requests for addition to the index can be found under proposed § 516.145. A description of the written report required in § 516.145 can be found under proposed § 516.143. Under proposed § 516.141 are provisions for drug companies to nominate a qualified expert panel as well as the panel's recordkeeping requirements. This section would also call for the submission of a written conflict of interest statement to FDA by each proposed panel member. Index holders would be able to modify their index listing under proposed § 516.161 or change drug ownership under proposed § 516.163. Requirements for records and reports are proposed under § 516.165.

*Description of Respondents:* Pharmaceutical companies that sponsor new animal drugs.

Thus, FDA estimates the burden for this collection of information as follows:



TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN<sup>1</sup>

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
516.119	2	1	2	1	2
516.121	30	2	60	4	240
516.123	3	1	3	8	24
516.125	2	3	6	20	120
516.129	30	2	60	12	720
516.141	20	1	20	8	160
516.143	20	1	20	80	1,600
516.145	20	1	20	12	240
516.161	1	1	1	4	4
516.163	1	1	1	2	2
516.165	10	2	20	8	160
Total					3,272

<sup>1</sup>There is no capital or operating and maintenance costs associated with this collection of information.

TABLE 2.—ESTIMATED ANNUAL RECORDKEEPING BURDEN<sup>1</sup>

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
516.141	30	2	60	0.5	30
516.165	10	2	20	1	20
Total					50

<sup>1</sup>There is no capital or operating and maintenance costs associated with this collection of information.

The burden estimate for this reporting requirement was derived by our Office of Minor Use and Minor Species Animal Drug Development by extrapolating from relevant portions of the current Investigational New Animal Drug (INAD) and NADA reporting requirements for similar actions by a similar segment of the regulated industry and from previous interactions with the minor species community.

In compliance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3507(d)), the agency has submitted the information collection provisions of this proposed rule to OMB for review.

## VII. Environmental Impact

We have carefully considered the potential environmental impacts of this rule and determined under 21 CFR 25.30(h) that this action is of a type that

does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

### **VIII. Federalism**

We have analyzed this proposed rule in accordance with the principles in Executive Order 13132. We have determined that the proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we have tentatively concluded that the proposed rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement has not been prepared.

### **IX. Comments**

You may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Please submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Identify your comments with the docket number found in brackets in the heading of this document. You may view received comments in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

### **List of Subjects**

#### *21 CFR Part 20*

Confidential business information, Courts, Freedom of information, Government employees.

*21 CFR Part 25*

Environmental impact statements, Foreign relations, Reporting and recordkeeping requirements.

*21 CFR Part 201*

Drugs, Labeling, Reporting and recordkeeping requirements.

*21 CFR Part 202*

Advertising, Prescription drugs.

*21 CFR Part 207*

Drugs, Reporting and recordkeeping requirements.

*21 CFR Part 225*

Animal drugs, Animal feeds, Labeling, Packaging and containers, Reporting and recordkeeping requirements.

*21 CFR Part 226*

Animal drugs, Animal feeds, Labeling, Packaging and containers, Reporting and recordkeeping requirements.

*21 CFR Part 500*

Animal drugs, Animal feeds, Cancer, Labeling, Packaging and containers, Polychlorinated biphenyls (PCBs).

*21 CFR Part 510*

Administrative practice and procedure, Animal drugs, Labeling, Reporting and recordkeeping requirements.

*21 CFR Part 511*

Animal drugs, Medical research, Reporting and recordkeeping requirements.

*21 CFR Part 515*

Administrative practice and procedure, Animal drugs, Confidential business information, Reporting and recordkeeping requirements.

*21 CFR Part 516*

Administrative practice and procedure, Animal drugs, Confidential business information, Reporting and recordkeeping requirements.

*21 CFR Part 558*

Animal drugs, Animal feeds.

*21 CFR Part 589*

Animal feeds, Animal foods, Food additives.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR Chapter I be amended as follows:

**PART 20—PUBLIC INFORMATION**

1. The authority citation for 21 CFR part 20 continues to read as follows:

**Authority:** 5 U.S.C. 552; 18 U.S.C. 1905; 19 U.S.C. 2531–2582; 21 U.S.C. 321–393, 1401–1403; 42 U.S.C. 241, 242, 242a, 242l, 242n, 243, 262, 263, 263b–263n, 264, 265, 300u–300u–5, 300aa–1.

2. Amend § 20.100 by adding paragraph (c)(44) to read as follows:

**§ 20.100 Applicability; cross-reference to other regulations.**

\* \* \* \* \*

(c) \* \* \*

(44) Minor-species drug index listings, in § 516.171 of this chapter.

**PART 25—ENVIRONMENTAL IMPACT CONSIDERATIONS**

3. The authority citation for 21 CFR part 25 continues to read as follows:

**Authority:** 21 U.S.C. 321–393; 42 U.S.C. 262, 263b–264; 42 U.S.C. 4321, 4332; 40 CFR parts 1500–1508; E.O. 11514, 35 FR 4247, 3 CFR, 1971 Comp., p. 531–533 as amended by E.O. 11991, 42 FR 26967, 3 CFR, 1978 Comp., p. 123–124 and E.O. 12114, 44 FR 1957, 3 CFR, 1980 Comp., p. 356–360.

4. Amend § 25.33 by revising paragraphs (a) introductory text, (c), (d) introductory text, and (g) to read as follows:

**§ 25.33 Animal drugs.**

\* \* \* \* \*

(a) Action on an NADA, abbreviated application, request for determination of eligibility for indexing, a supplement to such applications, or a modification of an index listing, if the action does not increase the use of the drug. Actions to which this categorical exclusion applies may include:

\* \* \* \* \*

(c) Action on an NADA, abbreviated application, request for determination of eligibility for indexing, a supplement to such applications, or a modification of an index listing, for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

(d) Action on an NADA, abbreviated application, request for determination of eligibility for indexing, a supplement to such applications, or a modification of an index listing, for:

\* \* \* \* \*

(g) Withdrawal of approval of an NADA or an abbreviated NADA or removal of a new animal drug from the index.

\* \* \* \* \*

## PART 201—LABELING

5. The authority citation for 21 CFR part 201 continues to read as follows:

**Authority:** 21 U.S.C. 321, 331, 351, 352, 353, 355, 358, 360, 360b, 360gg–360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

6. Amend § 201.105 by revising paragraphs (c)(2) and (d)(1) to read as follows:

### § 201.105 Veterinary drugs.

\* \* \* \* \*

(c) \* \* \*

(2) If the article is subject to section 512 or 572 of the act, the labeling bearing such information is the labeling authorized by the approved new animal drug application or contained in the index listing: *Provided, however,* That the information required by paragraph (c)(1) of this section may be omitted from the dispensing package if, but only if, the article is a drug for which directions, hazards, warnings, and use information are commonly known to veterinarians licensed by law to administer the drug. Upon written request, stating reasonable grounds therefore, the Commissioner will offer an opinion on a proposal to omit such information from the dispensing package under this proviso.

(d) \* \* \*

(1) Adequate information for such use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, and any relevant warnings, hazards, contraindications, side effects, and

precautions, and including information relevant to compliance with the new animal drug provisions of the act, under which veterinarians licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended, including all conditions for which it is advertised or represented; and if the article is subject to section 512 or 572 of the act, the parts of the labeling providing such information are the same in language and emphasis as labeling approved, permitted, or indexed under the provisions of section 512 or 572, and any other parts of the labeling are consistent with and not contrary to such approved, permitted, or indexed labeling; and

\* \* \* \* \*

7. Amend § 201.115 by revising paragraphs (a) and (b) to read as follows:

**§ 201.115 New drugs or new animal drugs.**

\* \* \* \* \*

(a) To the extent to which such exemption is claimed in an approved application with respect to such drug under section 505 or 512 of the act or an index listing with respect to such drug under section 572 of the act; or

(b) If no application under section 505 of the act is approved with respect to such drug but it complies with section 505(i), 512, or 572 of the act and regulations thereunder.

\* \* \* \* \*

8. Amend § 201.122 by revising paragraphs (a), (b), and (c) to read as follows:

**§ 201.122 Drugs for processing, repacking, or manufacturing.**

\* \* \* \* \*

(a) An approved new drug application or new animal drug application or a new animal drug index listing covers the production and delivery of the drug substance to the application or index listing holder by persons named in the

application or in the request for determination of eligibility for indexing, and, for a new drug substance, the export of it by such persons under § 314.410 of this chapter; or

(b) If no application is approved with respect to such new drug or new animal drug and it is not listed in the index, the label statement "Caution: For manufacturing, processing, or repackaging" is immediately supplemented by the words "in the preparation of a new drug or new animal drug limited by Federal law to investigational use", and the delivery is made for use only in the manufacture of such new drug or new animal drug limited to investigational use as provided in part 312 or § 511.1 or § 516.125 of this chapter; or

(c) A new drug application or new animal drug application or a request for addition to the index covering the use of the drug substance in the production and marketing of a finished drug product has been submitted but not yet approved, disapproved, granted, or denied, the bulk drug is not exported, and the finished drug product is not further distributed after it is manufactured until after the new drug application or new animal drug application is approved or the request for addition to the index is granted.

**PART 202—PRESCRIPTION DRUG ADVERTISING**

9. The authority citation for 21 CFR part 202 continues to read as follows:

**Authority:** 21 U.S.C. 321, 331, 352, 355, 360b, 371.

10. Amend § 202.1 by revising paragraph (e)(4)(i)(a) to read as follows:

**§ 202.1 Prescription-drug advertisements.**

\* \* \* \* \*

(e) \* \* \*



(4) *Substance of information to be included in brief summary.* (i)(a) An advertisement for a prescription drug covered by a new-drug application approved pursuant to section 505 of the act after October 10, 1962, or a prescription drug covered by a new animal drug application approved pursuant to section 512 of the act after August 1, 1969, or any approved supplement thereto, or for a prescription drug listed in the index pursuant to section 572 of the act, or any granted modification thereto, shall not recommend or suggest any use that is not in the labeling accepted in such approved new-drug application or supplement, new animal drug application or supplement, or new animal drug index listing or modification. The advertisement shall present information from labeling required, approved, permitted, or granted in a new-drug or new animal drug application or new animal drug index listing relating to each specific side effect and contraindication in such labeling that relates to the uses of the advertised drug dosage form(s) or shall otherwise conform to the provisions of paragraph (e)(3)(iii) of this section.

\* \* \* \* \*

#### **PART 207—REGISTRATION OF PRODUCERS OF DRUGS AND LISTING OF DRUGS IN COMMERCIAL DISTRIBUTION**

11. The authority citation for 21 CFR part 207 continues to read as follows:

**Authority:** 21 U.S.C. 321, 331, 351, 352, 355, 360, 360b, 371, 374, 381, 393; 42 U.S.C. 262, 264, 271.

12. Amend § 207.21 by revising the second sentence in paragraph (a) to read as follows:

**§ 207.21 Times for registration and drug listing.**

(a) \* \* \* If the owner or operator of the establishment has not previously entered into such an operation, the owner or operator shall register within 5 days after submitting a new drug application, abbreviated new drug application, new animal drug application, abbreviated new animal drug application, request for addition to the index, medicated feed mill license application, or a biologics license application. \* \* \*

\* \* \* \* \*

13. Amend § 207.35 by revising paragraph (b)(3)(v) to read as follows:

**§ 207.35 Notification of registrant; drug establishment registration number and drug listing number.**

\* \* \* \* \*

(b) \* \* \*

(3) \* \* \*

(v) The placing of the assigned NDC number on a label or in other labeling does not require the submission of a supplemental new drug application, supplemental new animal drug application, or a modification to an index listing.

\* \* \* \* \*

**PART 225—CURRENT GOOD MANUFACTURING PRACTICE FOR MEDICATED FEEDS**

14. The authority citation for 21 CFR part 225 continues to read as follows:

**Authority:** 21 U.S.C. 351, 352, 360b, 371, 374.

15. Amend § 225.1 by revising paragraph (c) to read as follows:

**§ 225.1 Current good manufacturing practice.**

\* \* \* \* \*

(c) In addition to the recordkeeping requirements in this part, Type B and Type C medicated feeds made from Type A articles or Type B feeds under approved NADAs or indexed listings and a medicated feed mill license are subject to the requirements of § 510.301 of this chapter.

16. Amend § 225.35 by revising paragraph (b) to read as follows:

**§ 225.35 Use of work areas, equipment, and storage areas for other manufacturing and storage purpose.**

\* \* \* \* \*

(b) Work areas and equipment used for the manufacture or storage of medicated feeds or components thereof shall not be used for, and shall be physically separated from, work areas and equipment used for the manufacture of fertilizers, herbicides, insecticides, fungicides, rodenticides, and other pesticides unless such articles are approved drugs, indexed drugs, or approved food additives intended for use in the manufacture of medicated feed.

17. Revise § 225.135 to read as follows:

**§ 225.135 Work and storage areas.**

Work areas and equipment used for the production or storage of medicated feeds or components thereof shall not be used for, and shall be physically separated from, work areas and equipment used for the manufacture and storage of fertilizers, herbicides, insecticides, fungicides, rodenticides, and other pesticides unless such articles are approved or index listed for use in the manufacture of animal feed.

## **PART 226—CURRENT GOOD MANUFACTURING PRACTICE FOR TYPE A MEDICATED ARTICLES**

18. The authority citation for 21 CFR part 226 continues to read as follows:

**Authority:** 21 U.S.C. 351, 352, 360b, 371, 374.

19. Amend § 226.1 by adding a second sentence to paragraph (b) to read as follows:

**§ 226.1 Current good manufacturing practice.**

\* \* \* \* \*

(b) \* \* \* Similarly, Type A medicated articles listed in the index are subject to the requirements of § 516.165 of this chapter.

**PART 500—GENERAL**

20. The authority citation for 21 CFR part 500 continues to read as follows:

**Authority:** 21 U.S.C. 321, 331, 342, 343, 348, 351, 352, 353, 360b, 371.

21. Amend § 500.25 by revising paragraph (c) to read as follows:

**§ 500.25 Anthelmintic drugs for use in animals.**

\* \* \* \* \*

(c) For drugs covered by approved new animal drug applications, the labeling revisions required for compliance with this section may be placed into effect without prior approval, as provided for in § 514.8 (d) and (e) of this chapter. For drugs listed in the index, the labeling revisions required for compliance with this section may be placed into effect without prior approval, as provided for in § 516.161(b)(1) of this chapter.

\* \* \* \* \*

22. Amend § 500.26 by revising paragraph (b) and the second sentence in paragraph (c) to read as follows:

**§ 500.26 Timed-release dosage form drugs.**

\* \* \* \* \*

(b) Timed-release dosage form animal drugs that are introduced into interstate commerce are deemed to be adulterated within the meaning of section 501(a)(5) of the act and subject to regulatory action, unless such animal

drug is the subject of an approved new animal drug application, or listed in the index, as required by paragraph (a) of this section.

(c) \* \* \* A new animal drug application or index listing is required in any such case.

\* \* \* \* \*

## PART 510—NEW ANIMAL DRUGS

23. The authority citation for 21 CFR part 510 continues to read as follows:

**Authority:** 21 U.S.C. 321, 331, 351, 352, 353, 360b, 371, 379e.

24. Amend § 510.301 by revising the introductory text, paragraph (a)(2), and the second sentence in paragraph (b)(1) to read as follows:

**§ 510.301** **Records and reports concerning experience with animal feeds bearing or containing new animal drugs for which an approved medicated feed mill license application is in effect.**

Records and reports of clinical and other experience with the new animal drug will be maintained and reported, appropriately identified with the new animal drug application(s) or index listing(s) to which they relate, to the Center for Veterinary Medicine in duplicate in accordance with the following:

(a) \* \* \*

(2) Information concerning any bacteriological or any significant chemical, physical, or other change or deterioration in the drug, or any failure of one or more distributed batches of the drug to meet the specifications established for it in the new animal drug application or request for determination of eligibility for indexing.

(b) \* \* \*

(1) \* \* \* *Unexpected* as used in this paragraph refers to conditions or developments not previously submitted as part of the new animal drug

application or in support of the index listing or not encountered during clinical trials of the drug, or conditions or developments occurring at a rate higher than shown by information previously submitted as part of the new animal drug application or in support of the index listing or at a rate higher than encountered during such clinical trials.

\* \* \* \* \*

25. Amend § 510.305 by revising paragraph (b) to read as follows:

**§ 510.305 Maintenance of copies of approved medicated feed mill licenses to manufacture animal feed bearing or containing new animal drugs.**

\* \* \* \* \*

(b) Approved or index listed labeling for each Type B and/or Type C feed being manufactured on the premises of the manufacturing establishment or the facility where the feed labels are generated.

26. Amend § 510.455 by revising paragraphs (b) and (c) to read as follows:

**§ 510.455 Requirements for free-choice medicated feeds.**

\* \* \* \* \*

(b) *What is required for new animal drugs intended for use in free-choice feed?* Any new animal drug intended for use in free-choice feed must be approved for such use under section 512 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360(b)) or listed in the index under section 572 of the act (21 U.S.C. 360ccc-1). Such approvals under section 512 of the act must be:

- (1) An original new animal drug application (NADA),
- (2) A supplemental NADA, or
- (3) An abbreviated NADA.

(c) *What are the approval requirements under section 512 of the act for new animal drugs intended for use in free-choice feed?* An approval under

section 512 of the act for a Type A medicated article intended for use in free-choice feed must contain the following information:

(1) Data, or reference to data in a master file (MF), showing that the target animal consumes the new animal drug in the Type C free-choice feed in an amount that is safe and effective (consumption/effectiveness data); and

(2) Data, or reference to data in an MF, showing the relevant ranges of conditions under which the drug will be chemically and physically stable in the Type C free-choice feed under field conditions.

\* \* \* \* \*

#### **PART 511—NEW ANIMAL DRUGS FOR INVESTIGATIONAL USE**

27. The authority citation for 21 CFR part 511 continues to read as follows:

**Authority:** 21 U.S.C. 321, 351, 352, 353, 360b, 371.

28. Amend § 511.1 by adding a paragraph (g) to read as follows:

**§ 511.1 New animal drugs for investigational use exempt from section 512(a) of the act.**

\* \* \* \* \*

(g) *Index of legally marketed unapproved new animal drugs for minor species.* All provisions of part 511 apply to new animal drugs for investigational use in support of indexing, as described in section 572 of the act, subject to the provisions of § 516.125 of this chapter.

#### **PART 515—MEDICATED FEED MILL LICENSE**

29. The authority citation for 21 CFR part 515 continues to read as follows:

**Authority:** 21 U.S.C. 360b, 371.

30. Amend § 515.10 by revising paragraphs (b)(4) and (b)(7) to read as follows:

**§ 515.10 Medicated feed mill license applications.**

\* \* \* \* \*

(b) \* \* \*

(4) A certification that the animal feeds bearing or containing new animal drugs are manufactured and labeled in accordance with the applicable regulations published under section 512(i) of the act or in accordance with the index listing published under section 572(e)(2) of the act.

\* \* \* \* \*

(7) A commitment that current approved or index listed Type B and/or Type C medicated feed labeling for each Type B and/or Type C medicated feed to be manufactured will be in the possession of the feed manufacturing facility prior to receiving the Type A medicated article containing such drug.

\* \* \* \* \*

31. Amend § 515.21 by revising paragraph (a)(3) to read as follows:

**§ 515.21 Refusal to approve a medicated feed mill license application.**

(a) \* \* \*

(3) The facility manufactures animal feeds bearing or containing new animal drugs in a manner that does not accord with the specifications for manufacture or labels animal feeds bearing or containing new animal drugs in a manner that does not accord with the conditions or indications of use that are published under section 512(i) or 572(e)(2) of the act.

\* \* \* \* \*

32. Part 516 is amended by adding subpart C, consisting of §§ 516.111 to 516.171, to read as follows:



**PART 516—NEW ANIMAL DRUGS FOR MINOR USE AND MINOR SPECIES****Subpart C—Index of Legally Marketed Unapproved New Animal Drugs for Minor Species**

## Sec.

- 516.111 Scope of this subpart.
- 516.115 Definitions.
- 516.117 Submission of correspondence under this subpart.
- 516.119 Permanent-resident U.S. agent for foreign requestors and holders.
- 516.121 Meetings.
- 516.123 Informal conferences regarding agency administrative actions.
- 516.125 Investigational use of minor species new animal drugs to support indexing.
- 516.129 Content and format of a request for determination of eligibility for indexing.
- 516.131 Refuse to file a request for determination of eligibility for indexing.
- 516.133 Denying a request for determination of eligibility for indexing.
- 516.135 Granting a request for determination of eligibility for indexing.
- 516.137 Notification of decision regarding eligibility for indexing.
- 516.141 Qualified expert panels.
- 516.143 Written report.
- 516.145 Content and format of a request for addition to the index.
- 516.147 Refuse to file a request for addition to the index.
- 516.149 Denying a request for addition to the index.
- 516.151 Granting a request for addition to the index.
- 516.153 Notification of decision regarding index listing.
- 516.155 Labeling of indexed drugs.
- 516.157 Publication of the index and content of an index listing.
- 516.161 Modifications to indexed drugs.

516.163 Change in ownership of an index file.

516.165 Records and reports.

516.167 Removal from the index.

516.171 Confidentiality of data and information in an index file.

**Authority:** 21 U.S.C. 360ccc-1, 371.

## **Subpart C—Index of Legally Marketed Unapproved New Animal Drugs for Minor Species**

### **§ 516.111 Scope of this subpart.**

This subpart implements section 572 of the act and provides standards and procedures to establish an index of legally marketed unapproved new animal drugs. This subpart applies only to minor species and not to minor use in major species. This index is only available for new animal drugs 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 and for new animal drugs intended for use only 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, where safety for humans is demonstrated in accordance with the standard of section 512(d) of the act (including, for an antimicrobial new animal drug, with respect to antimicrobial resistance). The index shall not include a new animal drug that is contained in, or a product of, a transgenic animal. Among its topics, this subpart sets forth the standards and procedures for:

- (a) Investigational exemptions for indexing purposes;
- (b) Submissions to FDA of requests for determination of eligibility of a new animal drug for indexing;
- (c) Establishment and operation of expert panels;

(d) Submissions to FDA of requests for addition of a new animal drug to the index;

(e) Modifications to index listings;

(f) Publication of the index; and

(g) Records and reports.

**§ 516.115 Definitions.**

(a) The following definitions of terms apply only in the context of subpart C of this part:

*Director* means the Director of the Office of Minor Use and Minor Species Animal Drug Development of the FDA Center for Veterinary Medicine.

*Holder* means the requestor of an index listing after the request is granted and the new animal drug is added to the index.

*Index* means FDA's list of legally marketed unapproved new animal drugs for minor species.

*Intended use* means the intended treatment, control or prevention of a disease or condition, or the intention to affect the structure or function of the body of animals within an identified species, subpopulation of a species, or collection of species.

*Qualified expert panel* means a panel that is composed of experts qualified by scientific training and experience to evaluate the target animal safety and effectiveness of a new animal drug under consideration for indexing.

*Requestor* means the person making a request for determination of eligibility for indexing or a request for addition to the index.

*Transgenic animal* means an animal whose genome contains a nucleotide sequence that has been intentionally modified in vitro, and the progeny of such an animal, provided that the term 'transgenic animal' does not include an

animal of which the nucleotide sequence of the genome has been modified solely by selective breeding.

(b) The definitions of the following terms are given in § 514.3 of this chapter:

Adverse drug experience.

Product defect/manufacturing defect.

Serious adverse drug experience.

Unexpected adverse drug experience.

**§ 516.117 Submission of correspondence under this subpart.**

Unless directed otherwise by FDA, all correspondence relating to any aspect of the new animal drug indexing process described in this subpart must be addressed to the Director of the Office of Minor Use and Minor Species Animal Drug Development. The initial correspondence for a particular index listing should include the name and address of the authorized contact person. Notifications of changes in such person or changes of address of such person should be provided in a timely manner.

**§ 516.119 Permanent-resident U.S. agent for foreign requestors and holders.**

Every foreign requestor and holder shall name a permanent resident of the United States as their agent upon whom service of all processes, notices, orders, decisions, requirements, and other communications may be made on behalf of the requestor or holder. Notifications of changes in such agents or changes of address of agents should preferably be provided in advance, but not later than 60 days after the effective date of such changes. The permanent-resident U.S. agent may be an individual, firm, or domestic corporation and may represent any number of requestors or holders. The name and address of the permanent-resident U.S. agent shall be submitted to the Director of the

Office of Minor Use and Minor Species Animal Drug Development and included in the index file.

**§ 516.121 Meetings.**

(a) A requestor or potential requestor is entitled to one or more meetings to discuss the requirements for indexing a new animal drug.

(b) Requests for such meetings should be in writing, be addressed to the Director, specify the participants attending on behalf of the requestor or potential requestor, and contain a proposed agenda for the meeting.

(c) Within 30 days of receiving a request for a meeting, FDA will attempt to schedule the meeting at a time agreeable to both FDA and the person making the request.

**§ 516.123 Informal conferences regarding agency administrative actions.**

(a) Should FDA make an initial decision denying a request for determination of eligibility for indexing, terminating an investigational exemption, determining that a qualified expert panel does not meet the selection criteria, denying a request for addition to the index, or removing a new animal drug from the index, FDA will give written notice that specifies the grounds for the initial decision and provides an opportunity for an informal conference for review of the decision.

(b) The written notice will include information for scheduling the informal conference and state that a written request for a conference must be made within 30 calendar days of the date FDA sends its notice.

(c) Within 30 days of receiving a request for an informal conference, FDA will attempt to schedule the meeting at a time agreeable to both FDA and the person making the request.

(d) Such an informal conference will be conducted by a presiding officer who will be the Director of the Center for Veterinary Medicine or his or her

designee, excluding the Director of the Office of Minor Use and Minor Species Animal Drug Development and other persons significantly involved in the initial decision.

(e) The person requesting an informal conference must provide a written response to FDA's initial decision at least 2 weeks prior to the date of the request for an informal conference. At the option of the person requesting an informal conference, such written response to FDA's initial decision may act in lieu of a face-to-face meeting. In this case, the informal conference will consist of a review by the presiding officer of the submitted written response.

(f) The purpose of an informal conference is to discuss scientific and factual issues. It will involve a discussion of FDA's initial decision and any written response to that decision.

(g) Internal agency review of a decision must be based on the information in the administrative file. If the person requesting an informal conference presents new information not in the file, the matter will be returned to the appropriate lower level in the agency for reevaluation based on the new information.

(h) Informal conferences under this part are not subject to the separation of functions rules in § 10.55 of this chapter.

(i) The rules of evidence do not apply to informal conferences. No motions or objections relating to the admissibility of information and views will be made or considered, but any party to the conference may comment upon or rebut all such data, information and views.

(j) The presiding officer will prepare a written summary of the informal conference and share it with the parties to the conference.

(k) The presiding officer will prepare a written report regarding the subject of the informal conference that states and describes the basis for his or her findings.

(l) The administrative record of the informal conference will consist of:

(1) The notice providing an opportunity for an informal conference and the written response to the notice.

(2) All written information and views submitted to the presiding officer at the conference or, at the discretion of the presiding officer, thereafter.

(3) The written summary of the informal conference.

(4) The presiding officer's written report.

(5) All correspondence and memoranda of any and all meetings between the participants and the presiding officer.

(m) The administrative record of the informal conference is closed to the submission of information and views at the close of the conference, unless the presiding officer specifically permits additional time for further submission.

(n) The administrative record of the informal conference specified herein constitutes the exclusive record for decision.

**§ 516.125 Investigational use of minor species new animal drugs to support indexing.**

(a) The investigational use of a new animal drug or animal feed bearing or containing a new animal drug intended solely for investigational use in minor species shall meet the requirements of part 511 of this chapter if the investigational use is for the purpose of:

(1) Demonstrating human food safety under section 572(a)(1)(B) of the act;

(2) Demonstrating safety with respect to individuals exposed to the new animal drug through its manufacture and use under section 572(c)(1)(F) of the act;

(3) Conducting an environmental assessment under section 572(c)(1)(E) of the act; or

(4) Obtaining approval of a new animal drug application or abbreviated new animal drug application under section 512(b) of the act.

(b) Correspondence and information associated with investigations described in paragraph (a) of this section shall not be sent to the Director, OMUMS, but shall be submitted to FDA in accordance with the provisions of part 511 of this chapter.

(c) The investigational use of a new animal drug or animal feed bearing or containing a new animal drug intended solely for investigational use in minor species, other than for an investigational use described in paragraph (a) of this section, shall meet the requirements of this section. For such investigations, all provisions of part 511 of this chapter apply with the following modifications:

(1) Under § 511.1(a)(1) of this chapter, the label statement is as follows:

*“Caution. Contains a new animal drug for investigational use only in laboratory animals or for tests in vitro in support of index listing. Not for use in humans.”*

(2) Under § 511.1(b)(1) of this chapter, the label statement is as follows:

*“Caution. Contains a new animal drug for use only in investigational animals in clinical trials in support of index listing. Not for use in humans. Edible products of investigational animals are not to be used for food for humans or other animals unless authorization has been granted by the U.S. Food and Drug Administration or by the U.S. Department of Agriculture.”*

(3) Under § 511.1(b)(4) of this chapter, the notice is titled “Notice of Claimed Investigational Exemption for a New Animal Drug for Index Listing” and is submitted in duplicate to the Director.



(4) Under § 511.1(c)(3) of this chapter, if an investigator is determined to be ineligible to receive new animal drugs, each “Notice of Claimed Investigational Exemption for a New Animal Drug for Index Listing” and each request for indexing shall be examined with respect to the reliability of information submitted by the investigator.

(5) Under § 511.1(c)(4) and (d)(2) of this chapter, with respect to termination of exemptions, the sponsor of an investigation shall not be granted an opportunity for a regulatory hearing before FDA pursuant to part 16 of this chapter. Instead, the sponsor shall have an opportunity for an informal conference as described in § 516.123.

(6) Under § 511.1(c)(5) of this chapter, if the Commissioner of Food and Drugs determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the data remaining are such that a request for addition to the index would have been denied, FDA will remove the new animal drug from the index in accordance with § 516.167.

(d) The investigational use of a new animal drug or animal feed bearing or containing a new animal drug subject to paragraph (c) of this section shall not be subject to the good laboratory practice requirements in part 58 of this chapter.

(e) Correspondence and information associated with investigations described in paragraph (c) of this section shall be sent to the Director of the Office of Minor Use and Minor Species in accordance with the provisions of this section.

**§ 516.129 Content and format of a request for determination of eligibility for indexing.**

(a) Each request for determination of eligibility:

(1) May involve only one drug (or one combination of drugs) in one dosage form;

(2) May not involve a new animal drug that is contained in or a product of a transgenic animal;

(3) May not involve the same drug in the same dosage form for the same intended use as a drug that is already approved or conditionally approved; and

(4) Must be submitted separately.

(b) A request for determination of eligibility for indexing may involve multiple intended uses and/or multiple minor species. However, if a request for determination of eligibility for indexing that contains multiple intended uses and/or multiple minor species cannot be granted in any part, the entire request will be denied.

(c) A requestor must submit two copies of a dated request signed by the authorized contact person for determination of eligibility for indexing that contains the following:

(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 proposed 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 (which includes on) 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 act and § 514.111 of this chapter (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 § 25.30 or § 25.33 of this chapter or an environmental assessment under § 25.40 of this chapter;

(10) Information sufficient to support the conclusion that the new animal drug is safe under section 512(d) of the 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.

**§ 516.131 Refuse to file a request for determination of eligibility for indexing.**

(a) If a request for determination of eligibility for indexing contains all of the information required by § 516.129, FDA shall file it, and the filing date shall be the date FDA receives the request.

(b) If a request for a determination of eligibility lacks any of the information required by § 516.129, FDA will not file it, but will inform the requestor in writing within 30 days of receiving the request as to what information is lacking.

**§ 516.133 Denying a request for determination of eligibility for indexing.**

(a) FDA will deny a request for determination of eligibility for indexing if it determines upon the basis of the request evaluated together with any other information before it with respect to the new animal drug that:

(1) The same drug in the same dosage form for the same intended use is already approved or conditionally approved;

(2) There is insufficient information to demonstrate 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 (which includes on) an early, non-food life stage of a food-producing minor species, and there is insufficient evidence to demonstrate safety for humans in accordance with the standard of section 512(d) of the act and § 514.111 of this chapter (including, for an antimicrobial new animal drug, with respect to antimicrobial resistance);

(3) The new animal drug is contained in or is a product of a transgenic animal;

(4) There is insufficient information 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;

(5) The requester fails to submit an adequate environmental assessment under § 25.40 of this chapter or fails to provide sufficient information to establish that the requested action is subject to categorical exclusion under § 25.30 or § 25.33 of this chapter;

(6) There is insufficient information to determine that the new animal drug is safe with respect to individuals exposed to the new animal drug through its manufacture or use; or

(7) The request for determination of eligibility for indexing fails to contain any other information required under the provisions of § 516.129.

(b) FDA may deny a request for determination of eligibility for indexing if it contains any untrue statement of a material fact or omits material information.

(c) When a request for determination of eligibility for indexing is denied, FDA will notify the requestor in accordance with § 516.137.

**§ 516.135 Granting a request for determination of eligibility for indexing.**

(a) FDA will grant the request for determination of eligibility for indexing if none of the reasons described in § 516.133 for denying such a request applies.

(b) When a request for determination of eligibility for indexing is granted, FDA will notify the requestor in accordance with § 516.137.

**§ 516.137 Notification of decision regarding eligibility for indexing.**

(a) Within 90 days after the filing of a request for a determination of eligibility for indexing based on § 516.129(c)(7)(i), or 180 days for a request

based on § 516.129(c)(7)(ii), FDA shall grant or deny the request, and notify the requestor of FDA's decision in writing.

(b) If FDA denies the request, FDA shall provide due notice and an opportunity for an informal conference as described in § 516.123 regarding its decision. A decision of FDA to deny a request for determination of eligibility for indexing following an informal conference shall constitute final agency action subject to judicial review.

**§ 516.141 Qualified expert panels.**

(a) *Establishment of a qualified expert panel.* Establishing a qualified expert panel is the first step in the process of requesting the addition of a new animal drug to the index. A qualified expert panel may not be established until FDA has determined that the new animal drug is eligible for indexing. The requestor must choose members for the qualified expert panel in accordance with selection criteria listed in paragraph (b) of this section and submit information about these proposed members to FDA. FDA must determine whether the proposed qualified expert panel meets the selection criteria prior to the panel beginning its work. Qualified expert panels operate external to FDA and are not subject to the Federal Advisory Committee Act, as amended, 5 U.S.C. App.

(b) *Criteria for the selection of a qualified expert panel.* (1) A qualified expert panel member must be an expert qualified by training and experience to evaluate the target animal safety and effectiveness of the new animal drug under consideration.

(2) A qualified expert panel member must certify that he or she has a working knowledge of section 572 of the act (the indexing provisions of the statute) and this subpart, and that he or she has also read and understood a

clear 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.

(3) A qualified expert panel member may not be an FDA employee.

(4) A qualified expert panel must have at least three members.

(5) A qualified expert panel must have members with a range of expertise such that the panel, as a whole, is qualified by training and experience to evaluate the target animal safety and effectiveness of the new animal drug under consideration.

(6) Unless FDA makes a determination to allow participation notwithstanding an otherwise disqualifying financial interest, a qualified expert panel member must not have a conflict of interest or the appearance of a conflict of interest, as described in paragraph (g) of this section.

(c) *Requestor responsibilities:* (1) The requestor must:

(i) Choose members for the qualified expert panel in accordance with selection criteria listed in paragraph (b) of this section.

(ii) Provide each potential expert panel member a copy of section 572 of the act (the indexing provisions of the statute) and this subpart and obtain certification that he or she has a working knowledge of the information.

(iii) Provide each potential expert panel member a written statement describing the purpose and scope of his or her participation on the qualified expert panel and obtain certification that he or she has read and understood the information. The written statement should describe the duties and responsibilities of qualified expert panels and their members established by paragraphs (e) and (f) of this section, including the need to prepare a written report under § 516.143.

(iv) Obtain information from each potential 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. This information can be obtained from a comprehensive curriculum vitae or similar document.

(v) Notify each potential expert panel member that he or she must submit information relating to potential conflict of interest directly to FDA in a timely manner, as required in paragraph (e)(6) of this section.

(2) The requestor must submit, in writing, the names and addresses of the proposed qualified expert panel members and sufficient information about each proposed member for FDA to determine whether the panel meets the selection criteria listed in paragraphs (b)(1) through (b)(5) of this section.

(3) After FDA has determined that the qualified expert panel meets the selection criteria, the requestor must provide to the panel all information known by the requestor that is relevant to a determination of the target animal safety and the effectiveness of the new animal drug at issue. In addition, the requestor must notify FDA of the name of the qualified expert panel leader.

(4) The requestor must immediately notify FDA if it believes a qualified expert panel member no longer meets the selection criteria listed in paragraph (b) of this section or is otherwise not in compliance with the requirements of this section.

(5) If a qualified expert panel member cannot complete the review for which he or she was selected, the requestor must either choose a replacement or justify the continued work of the panel in the absence of the lost panelist. In either case, the requestor must submit sufficient information for FDA to



determine whether the proposed revised qualified expert panel meets the selection criteria listed in paragraphs (b)(1) through (b)(5) of this section.

(6) The requestor must keep copies of all information provided to, or received from, qualified expert panel members, including the written report, for 2 years after the completion of the report, or the product is added to the index, whichever occurs later, and make them available to a duly authorized employee of the agency at all reasonable times.

(d) *FDA responsibilities.* (1) FDA will determine whether the requestor's proposed qualified expert panel meets the selection criteria listed in paragraph (b) of this section. FDA will expeditiously inform the requestor, in writing, of its determination. If FDA determines that the qualified expert panel does not meet the selection criteria, FDA will provide due notice and an opportunity for an informal conference as described in § 516.123. A determination by FDA that a proposed qualified expert panel does not meet the selection criteria following an informal conference shall constitute final agency action subject to judicial review.

(2) If FDA determines that a qualified expert panel no longer meets the selection criteria listed in paragraph (b) of this section or that the panel or its members are not in compliance with the requirements of this section, the agency will expeditiously inform the requestor, in writing, of this determination and provide due notice and an opportunity for an informal conference as described in § 516.123. A determination by FDA, following an informal conference, that a qualified expert panel no longer meets the selection criteria listed in paragraph (b) of this section or that the panel or its members are not in compliance with the requirements of this section shall constitute final agency action subject to judicial review.

(e) *Responsibilities of a qualified expert panel member.* A qualified expert panel member must do the following:

(1) Continue to meet all selection criteria described in paragraph (b) of this section.

(2) Act in accordance with generally accepted professional and ethical business practices.

(3) Review all information relevant to a determination of the target animal safety and effectiveness of the new animal drug provided by the requestor. The panel should also consider all relevant information otherwise known by the panel members, including anecdotal information.

(4) Participate in the preparation of the written report of the findings of the qualified expert panel, described in § 516.143.

(5) Sign, or otherwise approve in writing, the written report. Such signature or other written approval will serve as certification that the written report meets the requirements of the written report in § 516.143.

(6) Provide the information relating to potential conflict of interest described in paragraph (g) of this section to FDA for its consideration. Such information should be submitted directly to the Director when notified by the requestor.

(7) Immediately notify the requestor and FDA of any change in conflict of interest status.

(8) Certify at the time of submission of the written report that there has been no change in conflict of interest status, or identify and document to FDA any such change.

(f) *Additional responsibilities of a qualified expert panel leader.* (1) The qualified expert panel leader must ensure that the activities of the panel are

performed efficiently and in accordance with generally accepted professional and ethical business practices.

(2) The qualified expert panel leader serves as the principal point of contact between representatives of the agency and the panel.

(3) The qualified expert panel leader is responsible for submitting the written report and all notes or minutes relating to panel deliberations to the requestor.

(4) The qualified expert panel leader must maintain a copy of the written report and all notes or minutes relating to panel deliberations that are submitted to the requestor for 2 years after the report is submitted. Such records must be made available to a duly authorized employee of the agency for inspection at all reasonable times.

(g) *Prevention of conflicts of interest.* (1) For the purposes of this subpart, FDA will consider a conflict of interest to be any financial or other interest that could impair a person's objectivity in serving on the qualified expert panel or could create an unfair competitive advantage for a person or organization.

(2) Factors relevant to whether there is a conflict of interest or the appearance of a conflict of interest include whether the qualified expert panel member, their spouse, their minor children, their general partners, or any organizations in which they serve as an officer, director, trustee, general partner or employee:

(i) Is currently receiving or seeking funding from the requestor through a contract or research grant (either directly or indirectly through another entity, such as a university).

(ii) Has any employment, contractual, or other financial arrangement with the requestor other than receiving a reasonable fee for serving as a member of the qualified expert panel.

(iii) Has any ownership or financial interest in any drug, drug manufacturer, or drug distributor which will benefit from either a favorable or unfavorable evaluation or opinion.

(iv) Has any ownership or financial interest in the new animal drug being reviewed by the qualified expert panel.

(v) Has participated in the design, manufacture, or distribution of any drug that will benefit from either a favorable or unfavorable opinion of the qualified expert panel.

(vi) Has provided within 1 year any consultative services regarding the new animal drug being reviewed by the qualified expert panel.

(vii) Has entered into an agreement in which fees charged or accepted are contingent upon the panel member making a favorable evaluation or opinion.

(viii) Receives payment for services related to preparing information the requestor presents to the qualified expert panel, other than for services related to the written report described in § 516.143.

(3) To permit FDA to make a decision regarding potential conflict of interest, a potential qualified expert panel member must submit to the Director of the Office of Minor Use and Minor Species the following information relating to themselves, their spouse, their minor children, their general partners, or any organizations in which they 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:

(i) 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.

(ii) 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.

(iii) Consultant/advisor (current or under negotiation), including for each the following: Name of the firm, topic/issue, amount received, date initiated.

(iv) Contracts, grants, Cooperation Research and Development Agreement (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.

(v) Patents/royalties/trademarks, including for each the following: Description, name of firm involved, income received.

(vi) Expert witness (last 12 months or under negotiation), including for each the following: For or against, name of firm, issue, amount received.

(vii) Speaking/writing (last 12 months or under negotiation), including for each the following: Firm, topic/issue, amount received (honorarium/travel), date.

(viii) Whether the potential qualified expert panel member, their spouse, their minor children, their general partners or any organizations in which they serve as an officer, director, trustee, general partner or employee, have had, at any time in the past, involvement of the kind noted in paragraph (g)(3)(i)

through (g)(3)(vii) of this section with respect to the animal drug that is the subject of the qualified expert panel review.

(ix) 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 paragraph (g)(3)(i) through (g)(3)(viii) of this section.

(x) In all cases, a response of “no,” “none,” or “not applicable” is satisfactory when there is no relevant information to submit.

(xi) A certification statement signed by the potential qualified expert panel member to the effect that all information submitted is true and complete to the best of their knowledge, that they have read and understood their obligations as an expert panel member, and that they will notify FDA and the requestor of any change in their conflict of interest status.

(4) The fact that a qualified expert panel member receives a reasonable fee for services as a member of the qualified expert panel, 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.

**§ 516.143 Written report.**

The written report required in § 516.145(b)(3) shall:

(a) Be written in English by a qualified expert panel meeting the requirements of § 516.141;

(b) Describe the panel’s evaluation of all available target animal safety and effectiveness information relevant to the proposed use of the new animal drug, including anecdotal information;

(c) For all information considered, including anecdotal information, include either a citation to published literature or a summary of the information;

(d) State the panel's opinion regarding whether the benefits of using the new animal drug for the proposed use in a minor species outweigh its risks 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;

(e) Be signed, or otherwise approved in writing, by all panel members, in accordance with § 516.141; and

(f) If the panel unanimously concludes that the benefits of using the new animal drug for the proposed use in a minor species outweigh its risks 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, the written report shall:

(1) 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; and

(2) Include a recommendation regarding whether the new animal drug should be limited to use under the professional supervision of a licensed veterinarian.

**§ 516.145 Content and format of a request for addition to the index.**

(a) A requestor may request addition of a new animal drug to the index only after the new animal drug has been granted eligibility for indexing.

(b) A requestor shall submit two copies of a dated request signed by the authorized contact for addition of a new animal drug to the index that contains the following:

- (1) A copy of FDA's determination of eligibility issued under § 516.137;
- (2) A copy of FDA's written determination that the proposed qualified expert panel meets the selection criteria provided for in § 516.141(b);
- (3) A written report that meets the requirements of § 516.143;
- (4) A proposed index entry that contains the information described in § 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 and animal feeds bearing or containing such new animal drug according to current good manufacturing practices;
- (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; and
- (10) A draft Freedom of Information 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 other 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 qualified expert panel.

(v) For an early life stage of a food-producing minor species animal, a human food safety summary.

(c) Upon specific request by FDA, the requestor shall submit the information described in § 516.141 that it submitted to the qualified expert panel. Any such information not in English should be accompanied by an English translation.

**§ 516.147 Refuse to file a request for addition to the index.**

(a) If a request for addition to the index contains all of the information required by § 516.145(b), FDA shall file it, and the filing date shall be the date FDA receives the request.

(b) If a request for addition to the index lacks any of the information required by § 516.145, FDA will not file it, but will inform the requestor in writing within 30 days of receiving the request as to what information is lacking.

**§ 516.149 Denying a request for addition to the index.**

(a) FDA will deny a request for addition to the index if it finds the following:

(1) The same drug in the same dosage form for the same intended use is already approved or conditionally approved;

(2) On the basis of new information, the new animal drug no longer meets the conditions for eligibility for indexing;

(3) The request for indexing fails to contain information required under the provisions of § 516.145;

(4) The qualified expert panel fails to meet any of the selection criteria listed in § 516.141(b);

(5) The written report of the qualified expert panel and other information available to FDA is insufficient to permit FDA to determine that the benefits of using the new animal drug for the proposed use in a minor species outweigh its risks to the target animal, taking into account the harm caused by the absence of an approved or conditionally-approved new animal drug for the minor species in question;

(6) On the basis of the report of the qualified expert panel and other information available to FDA, the benefits of using the new animal drug for the proposed use in a minor species do not outweigh its risks to the target animal, taking into account the harm caused by the absence of an approved or conditionally-approved new animal drug for the minor species in question;  
or

(7) The request contains any untrue statement of a material fact or omits material information.

(b) When a request for addition to the index is denied, FDA will notify the requestor in accordance with § 516.153.

**§ 516.151 Granting a request for addition to the index.**

(a) FDA will grant the request for addition of a new animal drug to the index if none of the reasons described in § 516.149 for denying such a request applies.

(b) When a request for addition of a new animal drug to the index is granted, FDA will notify the requestor in accordance with § 516.153.

**§ 516.153 Notification of decision regarding index listing.**

(a) Within 180 days after the filing of a request for addition of a new animal drug to the index, FDA shall grant or deny the request and notify the requestor of FDA's decision in writing.

(b) If FDA denies the request for addition of a new animal drug to the index, FDA shall provide due notice and an opportunity for an informal conference as described in § 516.123. A decision of FDA to deny a request to index a new animal drug following an informal conference shall constitute final agency action subject to judicial review.

**§ 516.155 Labeling of indexed drugs.**

(a) The labeling of an indexed drug that is found to be eligible for indexing under § 516.129(c)(7)(i) shall state, prominently and conspicuously: "*NOT APPROVED BY FDA.—Legally marketed as an FDA indexed product. Extra-label use is prohibited.*" "*This product is not to be used in animals intended for use as food for humans or other animals.*"

(b) The labeling of an indexed drug that was found to be eligible for indexing for use in an early, non-food life stage of a food-producing minor species animal, under § 516.129(c)(7)(ii), shall state, prominently and conspicuously: "*NOT APPROVED BY FDA.—Legally marketed as an FDA indexed product. Extra-label use is prohibited.*"

(c) The labeling of an indexed drug shall contain such other information as may be prescribed in the index listing.

**§ 516.157 Publication of the index and content of an index listing.**

(a) FDA will make the list of indexed drugs available through the FDA Web site. A printed copy can be obtained by writing to the FDA Freedom of Information Staff or by visiting the FDA Freedom of Information Public Reading Room.

(b) The list will contain the following information for each indexed 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) Product labeling; and

(4) Conditions and any limitations that FDA deems necessary regarding use of the drug.

**§ 516.161 Modifications to indexed drugs.**

(a) After a drug is listed in the index, certain modifications to the index listing may be requested. Any modification of an index listing may not cause an indexed drug to be a different drug (or different combination of drugs) or a different dosage form. If such modification is requested, FDA will notify the holder that a new index listing is required for the new drug or dosage form.

(b) Modifications to the indexed drug will fall under one of three categories and must be submitted as follows:

(1) *Urgent changes.* (i) The following modifications to an indexed drug or its labeling should be made as soon as possible and a request to modify the indexed drug should be concurrently submitted:

(A) The addition to package labeling, promotional labeling, or prescription drug advertising of additional warning, contraindication, side effect, or cautionary information.

(B) The deletion from package labeling, promotional labeling, and drug advertising of false, misleading, or unsupported indications for use or claims for effectiveness.

(C) Changes in manufacturing methods or controls required to correct product or manufacturing defects that may result in serious adverse drug events.

(ii) The modifications described in paragraph (b)(1)(i) of this section must be submitted to the Director, Office of Minor Use and Minor Species Animal Drug Development in the form of a request for modification of an indexed drug, and must contain sufficient information to permit FDA to determine the need for the modification and whether the modification appropriately addresses the need.

(iii) FDA will take no action against an indexed drug or index holder solely because modifications of the kinds described in paragraph (b)(1)(i) of this section are placed into effect by the holder prior to receipt of a written notice granting the request if all the following conditions are met:

(A) A request to modify the indexed drug providing a full explanation of the basis for the modifications has been submitted, plainly marked on the mailing cover and on the request as follows: "Special indexing request—~~\_\_\_\_\_~~ modifications being effected;"

(B) The holder specifically informs FDA of the date on which such ~~\_\_\_\_\_~~ modifications are to be effected and submits two printed copies of any revised labeling to be placed in use, and

(C) All promotional labeling and all drug advertising are promptly revised consistent with modifications made in the labeling on or within the indexed drug package.

(2) *Significant changes.* (i) The following modifications to an indexed drug or its labeling may be made only after a request has been submitted to and subsequently granted by FDA:

(A) Addition of an intended use.

(B) Addition of a species.

(C) Addition or alteration of an active ingredient.

(D) Alteration of the concentration of an active ingredient.

(E) Alteration of dose or dosage regimen.

(F) Alteration of prescription or over-the-counter status.

(ii) Each modification described in paragraph (b)(2)(i) of this section must go through the same review process as an original index listing and is subject to the same standards for review.

(iii) Each submission of a request for a modification described in paragraph (b)(2)(i) of this section should contain only one type of modification unless one modification is actually necessitated by another, such as a modification of dose necessitated by a modification of the concentration of an active ingredient. Submissions relating to addition of an intended use for an existing species or addition of a species should be submitted separately, but each such submission may include multiple additional intended uses and/or multiple additional species.

(3) *Minor changes.* All modifications other than those described in paragraphs (b)(1) and (b)(2) of this section including, but not limited to, formulation, labeling, and manufacturing methods and controls (at the same level of detail that these were described in the request for determination of eligibility for indexing) must be submitted as part of the annual indexed drug experience report or as otherwise required by § 516.165.

(c) When changes affect the index listing, it will be updated accordingly.

**§ 516.163 Change in ownership of an index file.**

(a) A holder may transfer ownership of a drug's index file to another person.

(1) The former owner shall submit in writing to FDA a statement that all rights in the index file have been transferred, giving the name and address of the new owner and the date of the transfer. The former owner shall also

certify that a complete copy of the following, to the extent that they exist at the time of the transfer of ownership, has been provided to the new owner:

- (i) The request for determination of eligibility;
- (ii) The request for addition to the index;
- (iii) Any modifications to the index listing;
- (iv) Any records and reports under § 516.165; and
- (v) All correspondence with FDA relevant to the indexed drug and its index listing.

(2) The new owner shall submit the following information in writing to FDA:

- (i) The date that the change in ownership is effective;
- (ii) A statement that the new owner has a complete copy of all documents listed in paragraph (a)(1) of this section to the extent that they exist at the time of the transfer of ownership;
- (iii) A statement that the new owner understands and accepts the responsibilities of a holder of an indexed drug;
- (iv) The name and address of a new primary contact person or permanent-resident U.S. agent; and
- (v) A list of labeling changes associated with the change of ownership (e.g., a new trade name) as draft labeling, with complete final printed labeling to be submitted in the indexed drug annual report in accordance with §§ 516.161 and 516.165.

(b) Upon receiving the necessary information to support a change of ownership of a drug's index file, FDA will update its publicly-available listing in accordance with § 516.157.

**§ 516.165 Records and reports.**

(a) *Scope and purpose.* (1) The recordkeeping and reporting requirements of this section apply to all holders of indexed drugs, including indexed drugs intended for use in medicated feeds.

(2) A holder is not required to report information under this section if the holder has reported the same information under § 514.80 of this chapter.

(3) The records and reports referred to in this section are in addition to those required by the current good manufacturing practice regulations in parts 211, 225, and 226 of this chapter.

(4) FDA will review the records and reports required in this section to determine, or facilitate a determination, whether there may be grounds for removing a drug from the index under section 572(f) of the act.

(b) *Recordkeeping requirements.* (1) Each holder of an indexed drug must establish and maintain complete files containing full records of all information pertinent to the safety or effectiveness of the indexed drug. Such records must include information from foreign and domestic sources.

(2) The holder must, upon request from any authorized FDA officer or employee, at all reasonable times, permit such officer or employee to have access to copy and to verify all such records.

(c) *Reporting requirements.* (1) *Three-day indexed drug field alert report.* The holder must inform the appropriate FDA District Office or local FDA resident post of any product or manufacturing defects that may result in serious adverse drug events within 3 working days of first becoming aware that such a defect may exist. The holder may initially provide this information by telephone or other electronic communication means, with prompt written follow up. The mailing cover must be plainly marked "3-Day Indexed Drug Field Alert Report."



(2) *Fifteen-day indexed drug alert report.* The holder must submit a report on each serious, unexpected adverse drug event, regardless of the source of the information. The holder must submit the report within 15 working days of first receiving the information. The mailing cover must be plainly marked "15-Day Indexed Drug Alert Report."

(3) *Annual indexed drug experience report.* The holder must submit this report every year on the anniversary date of the letter granting the request for addition of the new animal drug to the index, or within 60 days thereafter. The report must contain data and information for the full reporting period. Any previously submitted information contained in the report must be identified as such. The holder may ask FDA to change the date of submission and, after approval of such request, file such reports by the new filing date. The report must contain the following:

(i) The number of distributed units of each size, strength, or potency (e.g., 100,000 bottles of 100 5-milligram tablets; 50,000 10-milliliter vials of 5-percent solution) distributed during the reporting period. This information must be presented in two categories: quantities distributed domestically and quantities exported. This information must include any distributor-labeled product.

(ii) If the labeling has changed since the last report, include a summary of those changes and the holder's and distributor's current package labeling, including any package inserts. For large-size package labeling or large shipping cartons, submit a representative copy (e.g., a photocopy of pertinent areas of large feed bags). If the labeling has not changed since the last report, include a statement of such fact.

(iii) A summary of any changes made during the reporting period in the methods used in, and facilities and controls used for, manufacture, processing, and packing. This information must be presented in the same level of detail that it was presented in the request for determination of eligibility for indexing. Do not include changes that have already been submitted under § 516.161.

(iv) Nonclinical laboratory studies and clinical data not previously reported under this section.

(v) Adverse drug experiences not previously reported under this section.

(vi) Any other information pertinent to safety or effectiveness of the indexed drug not previously reported under this section.

(4) *Distributor's statement.* At the time of initial distribution of an indexed drug by a distributor, the holder must submit a report containing the following:

(i) The distributor's current product labeling. This must be identical to that in the index listing except for a different and suitable proprietary name (if used) and the name and address of the distributor. The name and address of the distributor must be preceded by an appropriate qualifying phrase such as "manufactured for" or "distributed by."

(ii) A signed statement by the distributor stating:

(A) The category of the distributor's operations (e.g., wholesale or retail);

(B) That the distributor will distribute the drug only under the indexed drug labeling;

(C) That the distributor will promote the indexed drug only for use under the conditions stated in the index listing; and

(D) If the indexed drug is a prescription new animal drug, that the distributor is regularly and lawfully engaged in the distribution or dispensing of prescription products.

(5) *Other reporting.* FDA may by order require that a holder submit information in addition to that required by this section or that the holder submit the same information but at different times or reporting periods.

**§ 516.167 Removal from the index.**

(a) After due notice to the holder of the index listing and an opportunity for an informal conference as described in § 516.123, FDA shall remove a new animal drug from the index if FDA finds that:

(1) The same drug in the same dosage form for the same intended use has been approved or conditionally approved;

(2) The expert panel failed to meet the requirements in § 516.141;

(3) On the basis of new information before FDA, evaluated together with the evidence available to FDA when the new animal drug was listed in the index, the benefits of using the new animal drug for the indexed use do not outweigh its risks to the target animal, taking into account the harm caused by the absence of an approved or conditionally-approved new animal drug for the minor species in question;

(4) Any of the conditions in § 516.133(a)(2), (5), or (6) are present;

(5) The manufacture of the new animal drug is not in accordance with current good manufacturing practices;

(6) The labeling, distribution, or promotion of the new animal drug is not in accordance with the index listing;

(7) The conditions and limitations of use associated with the index listing have not been followed; or

(8) Any information used to support the request for addition to the index contains any untrue statement of material fact.

(b) The agency may partially remove an indexing listing if, in the opinion of the agency, such partial removal would satisfactorily resolve a safety or

effectiveness issue otherwise warranting removal of the listing under section 572(f)(1)(B) of the act.

(c) FDA may immediately suspend a new animal drug from the index if FDA determines that there is a reasonable probability that the use of the drug would present a risk to the health of humans or other animals. The agency will subsequently provide due notice and an opportunity for an informal conference as described in § 516.123.

(d) A decision of FDA to remove a new animal drug from the index following an informal conference, if any, shall constitute final agency action subject to judicial review.

**§ 516.171 Confidentiality of data and information in an index file.**

(a) For purposes of this section, the index file includes all data and information submitted to or incorporated by reference into the index file; such as data and information related to investigational use exemptions under § 516.125, requests for determination of eligibility for indexing, requests for addition to the index, modifications to indexed drugs, changes in ownership, reports submitted under § 516.165, and master files. The availability for public disclosure of any record in the index file shall be handled in accordance with the provisions of this section.

(b) The existence of an index file will not be disclosed by FDA before an index listing has been made public by FDA, unless it has previously been publicly disclosed or acknowledged by the requestor.

(c) If the existence of an index file has not been publicly disclosed or acknowledged, no data or information in the index file are available for public disclosure.

(d) If the existence of an index file has been publicly disclosed or acknowledged before an index listing has been made public by FDA, no data

or information contained in the file will be available for public disclosure before such index listing is made public, but the agency may, at its discretion, disclose a brief summary of such selected portions of the safety and effectiveness data as are appropriate for public consideration of a specific pending issue, e.g., at an open session of a Food and Drug Administration advisory committee or pursuant to an exchange of important regulatory information with a foreign government.

(e) After FDA sends a written notice to the requestor granting a request for addition to the index, the following data and information in the index file are available for public disclosure unless extraordinary circumstances are shown:

(1) All safety and effectiveness data and information previously disclosed to the public, as defined in § 20.81 of this chapter.

(2) A summary or summaries of the safety and effectiveness data and information submitted with or incorporated by reference in the index file. Such summaries do not constitute the full information described under section 572(c) and (d) of the act on which the safety or effectiveness of the drug may be determined. Such summaries will be based on the draft Freedom of Information summary submitted under § 516.145, which will be reviewed and, where appropriate, revised by FDA.

(3) A protocol for a test or study, unless it is shown to fall within the exemption established for trade secrets and confidential commercial information in § 20.61 of this chapter.

(4) Adverse reaction reports, product experience reports, consumer complaints, and other similar data and information, after deletion of the following:

(i) Names and any information that would identify the person using the product.

(ii) Names and any information that would identify any third party involved with the report, such as a veterinarian.

(5) A list of all active ingredients and any inactive ingredients previously disclosed to the public as defined in § 20.81 of this chapter.

(6) An assay method or other analytical method, unless it serves no regulatory or compliance purpose and is shown to fall within the exemption established in § 20.61 of this chapter.

(7) All correspondence and written summaries of oral discussions relating to the index file, in accordance with the provisions of part 20 of this chapter.

(f) The following data and information in an index file are not available for public disclosure unless they have been previously disclosed to the public as defined in § 20.81 of this chapter or they relate to a product or ingredient that has been abandoned and they no longer represent a trade secret or confidential commercial or financial information as defined in § 20.61 of this chapter:

(1) Manufacturing methods or processes, including quality control procedures.

(2) Production, sales, distribution, and similar data and information, except that any compilation of such data and information aggregated and prepared in a way that does not reveal data or information which is not available for public disclosure under this provision is available for public disclosure.

(3) Quantitative or semiquantitative formulas.

(g) Subject to the disclosure provisions of this section, the agency shall regard the contents of an index file as confidential information unless

specifically notified in writing by the holder of the right to disclose, to reference, or otherwise utilize such information on behalf of another named person.

(h) For purposes of this regulation, safety and effectiveness data include all studies and tests of an animal drug on animals and all studies and tests on the animal drug for identity, stability, purity, potency, and bioavailability.

(i) Safety and effectiveness data and information that have not been previously disclosed to the public are available for public disclosure at the time any of the following events occurs unless extraordinary circumstances are shown:

(1) No work is being or will be undertaken to have the drug indexed in accordance with the request.

(2) A final determination is made that the drug cannot be indexed and all legal appeals have been exhausted.

(3) The drug has been removed from the index and all legal appeals have been exhausted.

(4) A final determination has been made that the animal drug is not a new animal drug.

#### **PART 558— NEW ANIMAL DRUGS FOR USE IN ANIMAL FEEDS**

33. The authority citation for 21 CFR part 558 continues to read as follows:

**Authority:** 21 U.S.C. 360b, 371.

34. Amend § 558.3 by revising the last sentence of paragraph (b)(2) and revising paragraphs (b)(5), (b)(6), and (b)(7) to read as follows:

**§ 558.3 Definitions and general considerations applicable to this part.**

\* \* \* \* \*

(b) \* \* \*

(2) \* \* \* The manufacture of a Type A medicated article requires an application approved under § 514.105 of this chapter or an index listing granted under § 516.151 of this chapter.

\* \* \* \* \*

(5) A Type B or Type C medicated feed manufactured from a drug component (bulk or "drum-run" (dried crude fermentation product)) requires an application approved under § 514.105 of this chapter or an index listing granted under § 516.151 of this chapter.

(6) A "veterinary feed directive (VFD) drug" is a new animal drug approved under section 512(b) or listed in the index under section 572 of the Federal Food, Drug, and Cosmetic Act (the act) for use in or on animal feed. Use of a VFD drug must be under the professional supervision of a licensed veterinarian.

(7) A "veterinary feed directive" is a written statement issued by a licensed veterinarian in the course of the veterinarian's professional practice that orders the use of a veterinary feed directive (VFD) drug in or on an animal feed. This written statement authorizes the client (the owner of the animal or animals or other caretaker) to obtain and use the VFD drug in or on an animal feed to treat the client's animals only in accordance with the directions for use approved or indexed by the Food and Drug Administration (FDA). A veterinarian may issue a VFD only if a valid veterinarian-client-patient relationship exists, as defined in § 530.3(i) of this chapter.

\* \* \* \* \*

35. Amend § 558.5 by revising paragraphs (c) and (d) to read as follows:

**§ 558.5 Requirements for liquid medicated feed.**

\* \* \* \* \*



(c) *What is required for new animal drugs intended for use in liquid feed?*

Any new animal drug intended for use in liquid feed must be approved for such use under section 512 of the act or index listed under section 572 of the act. Such approvals under section 512 of the act must be:

- (1) An original NADA,
- (2) A supplemental NADA, or
- (3) An abbreviated NADA.

(d) *What are the approval requirements under section 512 of the act for new animal drugs intended for use in liquid feed?* An approval under section 512 of the act for a new animal drug intended for use in liquid feed must contain the following information:

(1) Data, or a reference to data in a master file (MF), that shows the relevant ranges of conditions under which the drug will be chemically stable in liquid feed under field use conditions; and

(2) Data, or a reference to data in an MF, that shows that the drug is physically stable in liquid feed under field conditions; or

(3) Feed labeling with recirculation or agitation directions as follows:

(i) For liquid feeds stored in recirculating tank systems: Recirculate immediately prior to use for not less than 10 minutes, moving not less than 1 percent of the tank contents per minute from the bottom of the tank to the top. Recirculate daily as described even when not used.

(ii) For liquid feeds stored in mechanical, air, or other agitation-type tank systems: Agitate immediately prior to use for not less than 10 minutes, creating a turbulence at the bottom of the tank that is visible at the top. Agitate daily as described even when not used.

36. Amend § 558.6 by revising paragraphs (a)(4)(iv) and (a)(6) to read as follows:

**§ 558.6 Veterinary feed directive drugs.**

(a) \* \* \*

(4) \* \* \*

(iv) Approved or index listed indications for use.

\* \* \* \* \*

(6) You must issue a VFD only for the approved or indexed conditions and indications for use of the VFD drug.

\* \* \* \* \*

**PART 589—SUBSTANCES PROHIBITED FROM USE IN ANIMAL FOOD OR FEED**

37. The authority citation for 21 CFR part 589 continues to read as follows:

**Authority:** 21 U.S.C. 321, 342, 343, 348, 371.

38. Revise § 589.1000 to read as follows:

**§ 589.1000 Gentian violet.**

The Food and Drug Administration has determined that gentian violet has not been shown by adequate scientific data to be safe for use in animal feed. Use of gentian violet in animal feed causes the feed to be adulterated and in violation of the Federal Food, Drug, and Cosmetic Act (the act), in the absence of a regulation providing for its safe use as a food additive under section 409 of the act, unless it is subject to an effective notice of claimed investigational exemption for a food additive under § 570.17 of this chapter, or unless the substance is intended for use as a new animal drug and is subject to an approved application under section 512 of the act, or an index listing under section 572 of the act, or an effective notice of claimed investigational

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exemption for a new animal drug under part 511 of this chapter or § 516.125  
of this chapter.

Dated: June 15, 2006

*Jeffrey Shuren*

Jeffrey Shuren,  
Assistant Commissioner for Policy.

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