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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: Final rule.

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 final regulations to implement section 572 of the act entitled "Index of Legally Marketed Unapproved New Animal Drugs for Minor Species." These regulations establish 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: This rule is effective [*insert date 75 days after date of publication in the* **Federal Register**].

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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 published final regulations implementing the designation provision of the act on July 26, 2007 (72 FR 41010) (the designation final 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 final regulations implementing the indexing provisions of the MUMS act. These regulations establish 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.

In the **Federal Register** of August 22, 2006 (71 FR 48840), FDA issued proposed regulations to implement section 572 of the act (21 U.S.C. 360ccc–1). The proposed rule initially provided for a 90-day public comment period during which the agency received several comments asserting that 90 days was not an adequate amount of time to prepare and submit meaningful comments. In response to this, in the **Federal Register** of October 2, 2006 (71 FR 57892), FDA extended the comment period allowing an additional 30 days of public comment.

II. Major Changes to the Proposed Rule

After considering public comments FDA has made the following changes to the proposed rule:

In § 516.123, paragraph (b) has been revised to read: "The written notice will include information for scheduling the informal conference and state that a written request for a conference must be made within 60 days of the date FDA sends its notice." Also, paragraph (c) has been revised to read: "Within 45 days of receiving a request for an informal conference, FDA will schedule and hold the informal conference at a time agreeable to both FDA and the person making the request."

In § 516.123, proposed paragraphs (j) and (l)(3) have been deleted and paragraph (k) has been revised to read: "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. Whenever time permits, the parties to the informal conference will have 30 days to review and comment on the report."

In section 516.141, paragraph (b)(1) has been revised to read: "A qualified expert panel member must be an expert qualified by training and experience

to evaluate a significant aspect of target animal safety or effectiveness of the new animal drug under consideration."

In addition, FDA has made two technical corrections to the proposed rule. The first one is in part 25 (21 CFR part 25). An amendment to § 25.33 was proposed as a conforming change to add index listed drugs to the list of actions for animal drugs which may be categorically excluded from the preparation of an environmental assessment. However, the agency neglected to propose a corresponding amendment to § 25.20 to also add index listed drugs to the list of actions requiring preparation of an environmental assessment. Therefore, this final rule contains a conforming change to § 25.20(m) to correct this omission. The second technical correction is in part 207 (21 CFR part 207). Amendments to §§ 207.21 and 207.35 were proposed as conforming changes to include index listed drugs under the drug registration and listing provisions of part 207. However, the agency neglected to propose a corresponding amendment to § 207.20(c) which describes who must register and submit a drug list. Therefore, this final rule contains a conforming change to § 207.20(c) to correct this omission.

III. Comments

The agency received comments from six organizations on the August 22, 2006, proposal. Comments were received from a trade organization representing new animal drug manufacturers, a trade organization representing pet product manufacturers, an animal feed manufacturer, a professional association representing veterinarians, an aquaculture trade association, and a U.S. Government agency.

All of the comments supported the purpose of the proposed regulations. Four comments generally supported the structure and scope of the proposed

regulations. Four comments expressed concern regarding the apparent complexity of the proposed regulations and encouraged the agency to demonstrate considerable flexibility in their implementation. The issue of greatest concern in these four comments involved the formation and functioning of the qualified expert panels proposed in the regulations—particularly the application of the conflict of interest provisions to potential panel members.

The agency understands the time and effort involved in providing comments on the proposed regulations and greatly appreciates this effort. The general issues noted previously, as well as a number of more specific issues raised in the comments, are addressed as follows:

(Comment 1) As noted, four comments expressed considerable concern over the apparent complexity of the process described in the proposed regulations. While most apparently accepted the need for this complexity as a direct consequence of the statutory requirements of section 572 of the statute, these comments uniformly expressed a desire that the agency be as flexible as possible in implementing the potentially more burdensome aspects of the regulations and encouraged the agency to provide as much guidance as possible to potential sponsors regarding their implementation.

(Response) The agency agrees that it should be flexible, to the extent allowable under the law, in implementing the indexing program. In order to further clarify the indexing process and assist requestors and potential requestors, the agency intends to develop guidance documents regarding various parts of the process as soon after finalization of implementing regulations as resources permit.

(Comment 2) One comment stated that the proposed indexing process is overly complex and too similar to the new animal drug approval process. This comment suggested that the proposed process be discarded and replaced with an alternative process that would emphasize general compounds rather than specific drug products.

(Response) The indexing process established by the MUMS act is for drug products rather than general compounds. For example, section 572(c)(1) of the act describes how to make a request for a determination of whether "a new animal drug" may be eligible for indexing. Moreover, that provision requires that the requestor submit information specific to a new animal drug, rather than for general compounds, such as information regarding the components and composition of the new animal drug and a description of the methods, facilities, and controls used for manufacturing the new animal drug. A request for addition to the index under section 572(d)(1) of the act is made "with respect to a new animal drug for which [FDA] has a made a determination of eligibility." Additionally, in considering a request for eligibility for indexing, the statute requires that the request 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.

Based on this and similar language in the statute, the agency believes, with respect to the indexing of new animal drugs, that indexing should follow the product-specific model of new animal drug approval.

However, the agency notes that this basic statutory construction does not necessarily preclude information supporting the indexing of one product from being used to support the indexing of other products, provided the information

is relevant to such products, and provided the party or parties gathering the information allow its use for that purpose if such information is proprietary.

(Comment 3) Four comments expressed concern about the formation and operation of qualified expert panels and, in particular, the application of the conflict of interest provisions of the regulations.

(Response) The agency is aware of the potential scarcity of experts to serve on some expert panels. It also wants to assure the integrity of this fundamental part of the indexing process, so that the agency can have confidence in the information and recommendations it receives from the expert panel and the public can trust the agency's decisions based on that information and recommendations.

The purpose of obtaining information regarding potential experts is to enable the agency to make an informed judgment, on a case-by-case basis, regarding whether a financial or other interest could impair the person's objectivity in serving on the panel or could create an unfair competitive advantage for a person or organization. Under the proposal, and not changed in the final rule, even if there is an otherwise disqualifying financial interest, FDA has discretion to nonetheless allow the person to serve as a member of the expert panel.

In making its determinations on the subject of conflicts of interest, the agency will be cognizant of both the need to assure the integrity of the expert panel process and the need to attract qualified experts to serve on these panels.

(Comment 4) Three comments suggested that the agency needs to consider the expertise of the entire panel as a whole, and not each panelist individually, when implementing the requirement that a panel be composed of "experts

qualified by training and experience to evaluate the safety and effectiveness of the new animal drug under consideration."

(Response) It is the intention of the agency to consider the expertise of the entire panel as a whole, as suggested in the comment. Proposed § 516.141(b)(5) says that the "panel, as a whole, is qualified by training and experience to evaluate the safety and effectiveness of the new animal drug under consideration." However, paragraph (b)(1) of the same regulation could be read as requiring that *each* individual member of a panel must meet this requirement, that is, each member of an expert panel is expected to be qualified to independently assess *all* aspects of a particular product's target animal safety *and* effectiveness. This was not the agency's intention and, therefore, the language of § 516.141(b)(1) has been revised to read: "A qualified expert panel member must be an expert qualified by training and experience to evaluate a significant aspect of target animal safety or effectiveness of the new animal drug under consideration."

(Comment 5) Two comments suggested that the scope of review of the expert panel might be expanded to include elements of food safety and/or environmental safety.

(Response) The MUMS act clearly established several distinct steps in the review process for indexing new animal drugs. One step is the determination of eligibility for indexing, which involves an evaluation of most of the indexing criteria, including food, user and occupational safety and environmental impacts. This evaluation is to be performed by the agency prior to the formation of a qualified expert panel. After the agency makes its determination regarding eligibility, a subsequent step is the formation and operation of a qualified expert panel. The responsibilities of the expert panel are set forth

in section 572(d)(2) of the act: Evaluate and make findings regarding target animal safety and effectiveness; provide information from which labeling can be written; and recommend whether the new animal drug should be over the counter, prescription, or veterinary feed directive.

Given this statutory construction, it would not be feasible or appropriate for the qualified expert panel to review or to comment upon aspects of product safety outside the scope of target animal safety and effectiveness. However, sponsors are free to involve experts, not serving in the capacity of qualified expert panel members, in the preparation of information submitted to the agency in support of a determination of eligibility for indexing.

(Comment 6) Several comments stated that 30 days is not a sufficient amount of time for a sponsor to submit a written response to the denial of a request for determination of eligibility for indexing or a denial of a request for indexing and indicated that this time period should be extended to 90 days.

(Response) While the agency agrees that 30 days may not be an adequate period for a written response to a denial, the agency also notes that the proposed regulation did not explicitly limit a sponsor to 30 days for a written response. Instead, it proposed that a sponsor must inform the agency within 30 days that it wishes to avail itself of the opportunity for an informal conference. Within 30 days of receipt of such a request, the agency would schedule such a conference at a time agreeable to both the agency and the sponsor, and the sponsor would be required to submit a written response at least two weeks prior to the scheduled meeting.

The agency continues to believe that it is appropriate to have a two-step process for scheduling an informal conference. This would involve an initial period of time during which a sponsor must signify their desire to have an

informal conference followed by a second period of time during which the conference will actually be scheduled. The agency also continues to believe that it needs to receive the written response from a sponsor a minimum of two weeks prior to an informal conference.

However, the agency has extended the initial period during which sponsors must request an informal conference from 30 days to 60 days to permit sponsors additional time to consider the need for such a conference. The agency has also extended the second period of time during which the agency will schedule a requested informal conference from 30 days to 45 days. With these revisions, a sponsor may take as long as 60 days to request an informal conference, may request that the conference not be held until 45 days after such a request and need not submit the written response in support of the conference until two weeks before the conference. This process will generally permit sponsors to have as much as 90 days to prepare a written response, if they feel they need it.

Accordingly, the language of § 516.123(b) and (c) is revised to read as follows:

(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 60 days of the date FDA sends its notice.

(c) Within 45 days of receiving a request for an informal conference, FDA will schedule and hold the informal conference at a time agreeable to both FDA and the person making the request.

(Comment 7) Two comments stated that the language of § 516.123 indicated that informal conferences were, in fact, rather formal and one

commentor asked for clarification of the reason for using the term "informal" in this context.

(Response) The statute and the proposed and final regulation use the phrase "informal conference." The agency believes that the purpose of the statutory use of the term "conference" in section 572 of the act is to be distinct from the term "hearing" which is used in the context of similar denial or withdrawal decisions regarding products involved in the new animal drug approval process under section 512 of the act. The hearing referred to in section 512 of the act has been clarified by regulation to be a formal evidentiary hearing under 21 CFR part 12. The agency believes that the purpose of the statutory use of the word "informal" in section 572 of the act is to draw a further distinction between the formal evidentiary hearing under 512 of the act and the informal conference under section 572.

FDA believes that the process for the informal conference set forth in § 516.123 is appropriately tailored. While much less formal than the part 12 hearings, it still ensures that there is a meaningful opportunity for parties to express their views, a neutral decision maker, and an administrative record for judicial review if the final agency decision is challenged in court. Moreover, by describing the process in a regulation, the parties in the informal conference will have a common understanding of how it will operate, fostering an orderly operation and reducing the potential for disagreements over the process.

(Comment 8) One comment questioned the inclusion of the requirement for an estimation of annual product distribution in proposed § 516.129(c)(6).

(Response) In accordance with section 572(c)(1)(A) of the act, the request for determination of eligibility for indexing must include the anticipated annual distribution of the new animal drug. This information would be useful,

for example, in estimating the extent of environmental and user exposure in the process of determining environmental and user safety.

(Comment 9) One comment suggested that requestors of an informal conference have an opportunity to read and respond to the minutes of an informal conference within 30 days.

(Response) This comment raises two issues which the agency needs to address and clarify in the final regulation. The first issue relates to whether the person requesting an informal conference should have the opportunity to review and comment on a summary of the informal conference. The agency believes that the requestor should have such an opportunity. In framing the comment in the context of the "minutes of an informal conference," the comment also raises an issue regarding what sort of a summary of the informal conference the person requesting an informal conference should have an opportunity to review and comment on. In this context, the agency has reconsidered the requirement in the proposed regulation for the preparation of both a "written summary" of the conference and a "written report" of the conference. The latter was intended to parallel the written report associated with a 21 CFR part 16 informal hearing, and was intended to be more comprehensive than simply a "written summary of the conference" or the "minutes of an informal conference" as expressed in the comment. The agency believes that the requestor of an informal conference should have an opportunity to review and comment on the written report of the informal conference. We have revised § 516.123(k) to provide for such a review whenever time permits. That being the case, the agency believes that a written summary of the informal conference is superfluous and this requirement,

which was proposed by means of §§ 516.123(j) and 516.123(l)(3), has been removed from the final regulation.

(Comment 10) Two comments requested clarification of different aspects of the early, non-food life-stage provision of the proposed regulations.

(Response) As stated in the preamble to the proposed regulations, the early, non-food life-stage provision of the statute and implementing regulations will be applicable only in limited circumstances, and the safety of food eventually derived from such animals will be determined in accordance with the safety standards of 512(d) of the act.

The agency has currently identified only early, non-food life stages of some aquatic species, such as certain fish eggs and mollusc larvae, as likely to be able to meet this standard. There is no explicit statutory restriction of this provision to aquatic minor species, although the statutory restriction to products intended only for use in a hatchery, tank, pond or other similar contained man-made structure tends to exclude terrestrial species. The agency has yet to identify a terrestrial species that it feels is likely to qualify under this provision of the statute, but has not ruled out the possibility that some terrestrial minor species could qualify.

The agency is unable at this time to establish any general criteria regarding ages, sizes, amount of time between early, non-food life stages and later food life stages, or biological developmental processes that can predict the applicability of this provision of the act. Nor is the agency able to make any general statements regarding how much information of what sort will be necessary to meet the requirements of 512(d) of the statute. These issues depend upon the drug and the minor species involved in each particular case.

(Comment 11) One comment asserted that the revenue to be expected from some segments of the minor species market may not justify the estimated administrative costs for indexing cited in the proposed rule. The comment is concerned with needed medicated feeds, especially for zoo and laboratory animals. The comment proposes that an "exemption" should be provided in cases where sales will not offset these costs. Specifically, the comment suggests that a threshold sales level should be set ($100,000 is recommended) above which indexing would be required, but below which an expanded policy of regulatory discretion would be provided.

The comment also notes that the inability to alter the nutrition and physical form of an approved medicated feed to suit use in a minor species limits the utility of the existing regulatory discretion policy (Compliance Policy Guide (CPG) 615.115) for the extra-label use of medicated feed in minor species. Therefore, it is suggested that a new policy of regulatory discretion based on customer formulated feeds be incorporated into the MUMS indexing rule for the intended uses that fall below the proposed sales threshold.

(Response) The lack of medicated feeds legally available to minor species is recognized by the agency. The Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA) (Pub. L. 103–396) provides for certain extra-label uses of new animal drugs by veterinarians, but specifically prohibits extra-label use of medicated feeds. The CPG is intended to be a limited exercise of regulatory discretion regarding access to needed medicated feeds for some minor species. The indexing provision was included in the MUMS act partly to address this concern. It is intended to provide *legal* means for sponsors to provide these much-needed formulations to non-food minor species animals, like the zoo species cited in this comment. The agency recognizes that indexing will not

provide for the legal availability of drugs for minor species under all circumstances. However, the exercise of regulatory discretion does not provide legal access under any circumstances.

The administrative cost of indexing, as cited in the proposed rule, is an estimate of the average cost of indexing a new animal drug. The enormous variety of species and products will be reflected in the range of complexity of indexing these products. Variables such as the number of species to be included in the intended use, the availability of scientific literature and experts, whether or not the drug has already been approved in other species or formulations, etc. will have a significant effect on the cost of completing a request for indexing. Simple requests for indexing can be expected to require less time to prepare and, therefore, will be less costly than the estimate, while others may be more involved and will require more time.

The agency will nonetheless continue to consider the exercise of regulatory discretion under appropriate circumstances and, as it gains experience with the indexing process, will consider whether it should make any changes to CPG 615.115.

(Comment 12) One comment was received in regard to the proposed conforming changes to parts 201 and 202 (21 CFR parts 201 and 202). This comment stated that the addition of indexing references to these parts of 21 CFR will add very specific requirements to the labeling and advertising process for an unapproved drug.

(Response) Part 201 pertains to drug labeling. The proposed conforming changes to part 201 are in subpart D which is entitled "Exemptions for Adequate Directions for Use." The regulations in this subpart describe situations where new drug and new animal drug labeling would be exempt

from the misbranding requirements of section 502(f)(1) of the act or provide clear descriptions of specific labeling information required to avoid misbranding under section 502(f)(1) of the act. Specifically, § 201.105 describes what information must appear on prescription new animal drug labeling and § 201.122 describes what information must appear on drugs for processing, packing, or manufacturing. The agency believes these same exemptions and clear descriptions should be available for index listed drugs and does not believe that the specific labeling requirements described in this subpart for approved new animal drugs are overly burdensome for index listed drugs. Furthermore, the labeling requirements for prescription new animal drugs described in § 201.105 are necessary for the safe and effective use of such drugs whether they are approved or index listed.

Part 202 pertains to prescription drug advertising. The conforming change to § 202.1 will require that prescription drug advertising for index listed drugs shall not recommend or suggest any use that is not in the labeling accepted in such index listing and that the advertisement shall present information from labeling granted in the listing relating to each specific side effect and contraindication in such labeling that relates to the uses of the advertised drug dosage form(s). Section 202.1 currently contains this same provision for new animal drugs that are approved under section 512 of the act and for new drugs that are approved under section 505 of the act. We do not believe this conformation to current regulations is unreasonable.

(Comment 13) One comment expressed confusion regarding whether unapproved index listed products that are drug listed under the provisions of part 207 (21 CFR part 207) are subject to product user fees under Animal Drug User Fee Act of 2003 (ADUFA).

(Response) Unapproved new animal drugs that are index listed under section 572 of the act are not subject to product user fees under ADUFA (Pub. L. 108–130). Unless specifically exempted, all new animal drugs that are in commercial distribution, whether approved or not, are subject to the drug listing requirements of part 207 (see § 207.20). However, to be subject to a product user fee, an animal drug product must not only be subject to the drug listing requirements of part 207, but also approved as either an animal drug application or supplemental animal drug application (see section 740(a)(2) of the act). As defined under ADUFA, these applications do not include drugs that are index listed under section 572 of the act (see section 739(1) and (2) of the act).

(Comment 14) One comment asked for clarification on why certain conforming changes to the regulations in part 510 for approved drugs were proposed to apply to index listed drugs.

(Response) Three sections in part 510 contain conforming changes. Those sections apply to new animal drugs, which means they apply to index listed drugs because they are new animal drugs. The conforming changes are needed so it is clear how these provisions apply in the context of index listed drugs. For example, § 510.301 describes the reporting and recordkeeping requirements for licensed medicated feed mills concerning experience with new animal drugs when used in or on animal feeds. Previously, the regulation said the records and report must be appropriately identified with the new animal drug application(s) to which they relate. The conforming amendment adds "or index listing(s)" to which they relate. Similarly, one of the items to be reported is any failure of the drug to meet specifications established for it in the new animal drug application. This is being amended to include specifications

established in the request for determination of eligibility for indexing. Conforming amendments are also made in § 510.305, which requires licensed medicated feed mill operators to maintain approved 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, and § 510.455, which describes the requirements for manufacturing a free-choice medicated animal feed.

(Comment 15) One comment stated that due to the prohibitive cost of production of small quantities of separately labeled product, the requirement for labeling indexed drugs separately from approved drugs could be a deterrent for indexing useful drugs that are already approved in major species. The comment suggested that adequate distinction could be required on existing labeling to provide the indexed claims as well as information on the approved labeling.

(Response) New animal drug labeling that contains information derived from both an application approved under section 512(b) of the act and from an index listing granted under section 572 of the act (572 index listing) would be misbranded under section 502(w)(2) of the act and would cause the new animal drug to be unsafe under section 512(a)(1)(A) and (C) of the act. Simply put, in this situation, the labeling information derived from the 512(b) approval does not conform with the 572 index listing, and the labeling information derived from the 572 index listing does not conform with the 512(b) approval. For example, under section 572(h) of the act, the labeling of an index listed drug must include the statement "NOT APPROVED BY FDA.—Legally marketed as an FDA indexed product." Such a statement would be false on

the labeling of a product approved under section 512(b) of the act because that product has been approved by FDA.

(Comment 16) One comment requested clarification on the statement in proposed § 516.155 to the effect that a product cannot be utilized in an extra-label manner once it is indexed. The comment said that this could be prohibitive to the veterinarian's ability to utilize an approved medication off label when needed if it has also been indexed.

(Response) Under § 516.155, the label of an indexed drug must state that extra-label use is prohibited. This statement is based on section 572(h) of the act. However, this statement prohibiting extra-label use of new animal drugs indexed under section 572 of the act does not impose any restrictions, beyond those that already existed, on the extra-label use of new animal drugs approved under section 512(b) of the act.

The extra-label use of an approved new animal drug is not permitted when "the labeling of another animal drug that contains the same active ingredient which is in the same dosage form and concentration" provides for the same use as a contemplated extra-label use (section 512(a)(4)(A) of the act). We believe that the reference to "another animal drug" in this provision means a new animal drug that, like the drug to be used in an extra-label manner, has been approved under section 512(b) of the act, and that it does not include a new animal drug that has been indexed under section 572 of the act. The regulations implementing the extra-label use provisions of section 512 of the act provide that one of the conditions for the extra-label use of an approved new animal drug is that "there is no *approved* new animal drug that is labeled for such use and that contains the same active ingredient which is in the required dosage form and concentration" (§§ 530.20(a)(1) (emphasis added)

and 530.30(a)). Based on our interpretation of the act, we do not believe the condition in this regulation should be broadened to reference indexed drugs along with approved drugs. Thus, if a new animal drug is index listed for intended use A, for example, and the same active ingredient in the same dosage form is approved for intended use B, then the approved drug may be used in an extra-label manner for intended use A, as long as all other provisions of 21 CFR part 530 have been met.

(Comment 17) One comment noted that the preamble failed to explicitly state that indexed drugs may fall into one of three categories: Over-the-counter, prescription, and veterinary feed directive (VFD).

(Response) We agree that index listed drugs may fall into one of these three categories. Prescription status for index listed drugs is provided for in section 503(f)(1)(A)(ii) of the act and VFD status is provided for in section 504(a)(1) of the act. The current regulations in title 21 of the CFR have been revised accordingly by conforming change in this rulemaking at § 201.105, § 202.1, § 558.3, and § 558.6.

(Comment 18) One comment stated that it appears that there can be a number of holders of the same product listed in the index, in other words, there is no exclusivity associated with index listing.

(Response) We agree. There are no exclusive marketing rights associated with index listed drugs, such as are provided for MUMS-designated approved and conditionally approved drugs under section 573(c) of the act.

(Comment 19) One comment requested clarification regarding whether proposed § 516.125(d) meant that target animal safety studies done under an index investigational new animal drug (INAD) were not required to be conducted in accordance with good laboratory practices (GLPs).

(Response) While the agency encourages adherence to GLPs to the maximum extent possible, the comment is correct that target animal safety studies in support of an index listing are not required to be conducted under GLPs. Qualified expert panels may consider all available information in reaching their conclusions regarding target animal safety and effectiveness, including target animal safety studies that do not meet the GLP standards of 21 CFR part 58.

(Comment 20) One comment stated that the agency's estimated costs to a MUMS index drug requestor appeared to be reasonable and accurate. However, the comment also stated that, as a result of the fees referred to in § 516.141(g)(4), costs for complex reviews requiring extensive panel time may be dramatically higher than simple reviews that can be quickly completed. The comment suggested that, in an effort to contain such costs, avoid economic discrimination, and increase participation in the indexing process, the agency should consider, at least for an initial period of time, establishing a uniform fee of $10,000 for indexing requests.

(Reponse) FDA anticipates that some expert panel members may charge requestors a fee for their professional services. § 516.141(g)(4) recognizes this fact and states that if such professional fees are paid they should be no more than commensurate with the value of the time that the member devotes to the review process in order to avoid a conflict of interest or the appearance of a conflict of interest. This cost to requestors is also discussed in the Analysis of Economic Impacts section of the proposed rule and this final rule. While the agency supports, in principle, efforts to contain costs and increase efficient utilization of the indexing process, the agency believes that, § 516.141(g)(4) notwithstanding, it should not be involved in establishing or otherwise

regulating fees for the work expert panel members provide to the requestor as part of the indexing process.

(Comment 21) One comment suggested that a requestor not necessarily be a particular firm, but potentially a group of individuals or organizations each of which could contribute to the indexing process.

(Response) Under the new animal drug approval process, information gathered from multiple sources can be placed into master files from which the information can be referenced in support of one or more new animal drug applications. Master files can contain public or proprietary information relating to, for example, manufacturing processes. The indexing rule does not prevent different individuals or groups from contributing to the indexing of a drug product using this type of a master file mechanism, and FDA intends to allow for such master files to be used in the context of indexing.

(Comment 22) One comment requested clarification of the post-indexing reporting requirements for chemistry, manufacturing, and control (CMC) information and whether they will be the same as the Minor Changes and Stability Reporting (MCSR) process.

(Response) MCSR, as required by 21 CFR 514.8(b)(4), does not apply to indexed drugs. Under § 516.161(b)(1), changes in manufacturing methods or controls required to correct product or manufacturing defects that may result in serious adverse drug events should be made as soon as possible and a request to modify the indexed drug should be concurrently submitted to the Director, Office of Minor Use and Minor Species Animal Drug Development (OMUMS). Under § 516.165(c)(3)(iii), the annual indexed drug experience report must contain 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. The information is not included in this report, however, if it has already been submitted under § 516.161.

(Comment 23) One comment stated that proposed § 516.165(a)(3) appeared to be inconsistent with proposed § 516.165(c)(3)(iii) in that § 516.165(a)(3) implied that indexed drugs must meet all "approved CMC requirements" while § 516.165(c)(3)(iii) implied that CMC information only needed to be reported in the level of detail it was originally described in the indexing request.

(Response) The comment is correct that under § 516.165(c)(3)(iii), changes in the manufacturing process subsequent to product indexing need to be reported only to the level of detail that the manufacturing process was described in the original request for a determination of eligibility for indexing. However, section 572(d)(1)(F) of the act requires, as a condition of indexing, that requestors affirmatively commit to manufacture the drug product proposed for indexing according to current good manufacturing practices (cGMP). Accordingly, § 516.165(a)(3) reflects the requirement for the manufacturer of an indexed drug to meet the record-keeping requirements of the cGMP regulations, and that this requirement is *in addition* to annually reporting the relatively limited CMC information required by § 516.165.

(Comment 24) One comment indicated that, with respect to occupational and user safety, the proposed regulations provided "no regulatory relief from the statutory requirement for an indexed drug."

(Response) This is an accurate observation. The regulations, §§ 516.129(c) and 516.133(a), are consistent with section 572(c)(1)(F) and (c)(2)(E) of the act in this regard. Both the regulations and the statutory provisions they

implement require that this aspect of product safety be assessed in accordance with the requirements of section 512(d) of the act.

(Comment 25) One comment stated that references to "statutory criteria" in the preamble were unclear, raising the question whether the qualified expert panel and the agency would be subject to the evidentiary standards of section 512 or to those of section 572.

(Response) The comment failed to specifically identify where in the preamble the unclear references to statutory criteria appeared, but the agency presumes that it was in the introductory paragraph of section II. F. (71 FR 48840 at 48842 and 48843). This paragraph describes the two-part indexing review process established by the act, which includes a review of whether the new animal drug meets the statutory criteria regarding target animal safety and effectiveness.

The standard for target animal safety and effectiveness is established, with respect to expert panels, under section 572(d)(2)(C) of the act and, with respect to the agency, under section 572(d)(4) as: 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.

IV. Conforming Changes

Conforming changes to certain applicable sections of title 21 of the Code of Federal Regulations (CFR) can be found in:

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

§ 25.20 *Actions requiring preparation of an environmental assessment.*

§ 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.*

V. Legal Authority

FDA's authority for issuing this final 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 final rule. Section 701(a) authorizes the agency to issue regulations for the efficient enforcement of the act.

VI. Analysis of Economic Impacts

FDA has examined the impacts of the final 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 finds that the final 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 $476,000 in the first year to about $869,000 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 establishing "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 $127 million, using the most current (2006) implicit price deflator for the gross domestic product. FDA does not expect this final 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.

A. Summary

The final rule is expected to result in about 30 requests for a determination of eligibility for indexing for 60 products annually, or 2 per requestor. 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.

B. Comments on Proposed Rule

FDA received six comments to the proposed rule, none of which contained substantive comments on the methodology used in the analysis of impacts of the proposed rule. As such, we have retained the methodology for the analysis of the final rule. Our requests in the analysis of impacts section of the proposed rule for additional cost data did not elicit any data that conflicted with our estimates. We did, however, receive one comment that suggested the paperwork reporting burden may be too low. We revised the economic impacts

associated with the paperwork reporting burden, as well as made other small changes to the final rule due to other public comments. We address comments on individual components and any changes made to the final rule in the administrative cost section.

C. 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 animal drugs that are marginally economically viable could use this system to avoid the traditional animal drug approval process. Under this final 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.

D. Administrative Costs

This section will describe and estimate the annual administrative costs by 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 final rule were determined by Center for Veterinary Medicine (CVM) personnel for the proposed rule. Labor hour estimates for some procedure have been amended in this final rule due to public comments.

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[1]. 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 agent 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.

Section 516.121 of the final rule 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.

Section 516.123 concerns informal conferences regarding agency administrative actions. These would include conferences to discuss a request for determination of eligibility 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. In response to public comments, we have provided for a 60-day time period for industry to respond with a written request for

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

a conference, rather than the proposed 30-day time period. Additionally, we have amended the final rule to require that an informal conference be scheduled and held within a 45-day period from our receipt of a request for an informal conference. The proposed rule would have required that we only attempt to schedule and hold the conference within 30 days. We do not expect these two changes to have an impact on the cost estimates of this provision. We estimate that about three requestors would request one conference with us 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 (§ 516.123) 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 section 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. Based on a public comment that the paperwork burden was underestimated in the proposed rule, we have increased the number of labor hours for preparing each request from 12 to 20. At the loaded wage estimate of $42.29 per hour, this provision would require about 1,200 hours equal to about $50,700. Included

in this estimate of 60 requests are any resubmitted requests that were previously denied.

Section 516.141 requires 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. We are 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 16 hours of effort by regulatory affairs personnel. This figure has been increased from the 8 hours estimated in the proposed rule based on a public comment. At the same loaded wage estimate, these 320 hours are estimated at about $13,500 annually. An additional 0.5 hours is estimated for recordkeeping for the creation of the qualified panels described in § 516.141. This would result in an additional $400 in annual costs.

Section 516.143 describes how the expert panel will 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 120 hours, an increase from the 80 hours estimated for the proposed rule. This equates to 2,400 hours for 20 panels. The rule allows for fees to be paid to panel members for their time. We estimate 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 $300,000 annually for the total industry, or $15,000 per requestor for each animal drug under consideration.

We estimate that the formal request for addition to the index, provided for in § 516.145, will require about 20 hours to prepare, an increase from the 12 hours estimated in the proposed rule. This will result in another 400 hours of effort (20 requests times 20 hours) for regulatory affairs personnel. We project the compliance cost of this effort at $16,900 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 will cost about $250 in the first year. Total modification requests and ownership change notifications are expected to increase by one 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 final rule will 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 will 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) will require an additional hour of administrative time for each indexed drug listing. These additional 20 hours will 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 $407,000 in the first year. This represents an increase of $134,000 from the $273,000 estimated cost of the proposed rule. These costs will be borne by 30 firms that make a request for determination of eligibility for indexing at an average cost per requestor of about $13,600 per submission. Including only those estimated 20 firms that followup with a request for addition to the index, we project average costs at about $19,000. Costs in succeeding years would be expected to increase slightly due to the annual reporting requirements for all indexed drugs, resulting in year–10 total costs for the industry at about $492,000.

E. Costs to Government

The Government would also incur costs for this final 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 final rule would be the sum of private administrative and Government costs. Total costs are estimated to increase from $476,000 in the first year up to $869,000 in the 10th year.

F. 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 final 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 use 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 fewer than 750 employees. Census data shows that

723 companies with 901 establishments represent this category.[2] 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 $19,000. This cost per request represents about 2.1 percent of the revenues of the smallest set of establishments (those establishments with 1 to 4 employees), and 0.5 percent or less of revenues of all larger establishments.[3] These costs would not represent a significant economic impact on the firms expected to request an index listing, 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 final rule that would accomplish the objective while minimizing significant impacts of the rule. As stated previously, the agency believes that the final rule, due to the relatively small size of the costs, would

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[2]2002 Economic Census, U.S. Census Bureau, Manufacturing Industry Series, Pharmaceutical Preparation Manufacturing, tables 3 and 4.

[3]U.S. Department of Labor, Bureau of Labor Statistics. 2002 revenues inflated to 2007 dollars using the CPI-U.

not be likely to impose significant economic impacts on a substantial number of small entities.

The statute that creates this system, Public Law 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 final rule achieves the objective of increasing the number of drugs that can be legally marketed for minor species with minimal costs to industry while staying within the limits set by Public Law 108–282.

VII. Paperwork Reduction Act of 1995

This final 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 (44 U.S.C. 3501–3520). A description of these provisions is given below with an estimate of the annual reporting 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.

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 final rule implements 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 final 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 (21 CFR part 516), § 516.119 provides requirements for naming a permanent-resident U.S. agent by foreign drug companies, and § 516.121 provides for informational meetings with FDA. Section 516.123 provides requirements for requesting informal conferences regarding agency administrative actions and § 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 § 516.129 and provisions for subsequent requests for addition to the index can be found under § 516.145. A description of the written report required in § 516.145 can be found under § 516.143. Under § 516.141 are provisions for drug companies to nominate a qualified expert panel as well as the panel's recordkeeping requirements. This section also calls for the submission of a written conflict of interest statement to FDA by each proposed panel member. Index holders are able to modify their index listing under § 516.161 or change drug ownership under § 516.163. Requirements for records and reports are under § 516.165.

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

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

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]

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	20	1,200
516.141	20	1	20	16	320
516.143	20	1	20	120	2,400
516.145	20	1	20	20	400
516.161	1	1	1	4	4
516.163	1	1	1	2	2
516.165	10	2	20	8	160
Total					4,872

[1]There is no capital or operating and maintenance cost associated with this collection of information.

TABLE 2.—ESTIMATED ANNUAL RECORDKEEPING BURDEN1

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

[1]There is no capital or operating and maintenance cost associated with this collection of information.

FDA announced that the proposed rule contained information collection provisions that were subject to review by OMB under the Paperwork Reduction Act of 1995 and invited public comment in the **Federal Register** of August 22, 2006 (71 FR 48840). In response to that notice FDA received two comments concerning the estimated paperwork reporting burden. One comment said that the estimates appear to be reasonable and accurate while the other comment said that some were potentially underestimated. Specifically, the second comment felt that the agency's estimates for the hours per response were too low for the time required for creation of an expert panel by regulatory professionals in § 516.141 and for the time required to prepare the written report in § 516.143. Although the comment did not offer new estimates for

these sections, FDA agrees that these estimates may be too low. Therefore, FDA believes that 16 hours is a more reasonable response time required for creation of an expert panel. In view of increased reporting requirements under § 516.141, CVM has increased the "Hours per Response" under this citation in "Table 1. Estimated Annual Reporting Burden," from 8 to 16 hours thereby increasing the total burden hours to 320. FDA also believes that 120 hours is a more reasonable response time required to prepare the written report. In view of increased reporting requirements under § 516.143, CVM has increased the "Hours per Response" under this citation in "Table 1. Estimated Annual Reporting Burden," from 80 to 120 hours thereby increasing the total burden hours to 2400.

The second comment also proposed 20 to 80 hours of response time for preparation of a request for determination of eligibility and 20 to 80 hours of response time for preparation of a request for addition to the index. FDA agrees, in light of both comments, that 20 hours is a more reasonable response time required to prepare each of these two submissions. In view of increased reporting requirements under § 516.129, CVM has increased the "Hours per Response" under this citation in "Table 1. Estimated Annual Reporting Burden," from 12 to 20 hours thereby increasing the total burden hours to 1,200. For § 516.145, CVM has also increased the "Hours per Response" in "Table 1. Estimated Annual Reporting Burden," from 12 to 20 hours thereby increasing the total burden hours for this section to 400.

The second comment also requested clarification on the time allotted for the notice of claimed investigational exemption in § 516.125. This reporting burden accounts for the time required to prepare information pertinent to the

safety or effectiveness of a drug derived from investigational studies for review by the expert panel.

Finally, it should be noted that FDA received no comment on the proposed conforming changes to 21 CFR 515.10(b) which describes what information must be contained in a medicated feed mill license application. Accordingly, the agency is revising Form FDA 3448 Medicated Feed Mill License Application (OMB No. 0910–0337) to reflect these minor conforming changes. This revision will not change the information reporting burden already approved for this form. It merely revises one of the certifications to reflect the fact that new animal drugs now include index listed drugs.

The information collection provisions of this final rule have been submitted to OMB for review. Prior to the effective date of this final rule, FDA will publish a notice in the **Federal Register** announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this final rule. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

VIII. Environmental Impact

We have carefully considered the potential environmental impacts of this final 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.

IX. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the 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, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

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, 21 CFR Chapter I is 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 § 25.20 by revising paragraph (m) to read as follows:

§ 25.20 Actions requiring preparation of an environmental assessment.

* * * * *

(m) Approval of NADA's, abbreviated applications, supplements, actions on INAD's, and granting of requests for determination of eligibility for indexing, unless categorically excluded under § 25.33 (a), (c), (d), or (e).

* * * * *

■ 5. 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

■ 6. 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.

■ 7. 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

* * * * *

■ 8. 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 or 512 of the act is approved and no request for addition to the index is granted under section 572 with respect to such drug but it complies with section 505(i), 512(j), or 572(g) of the act and regulations thereunder.

* * * * *

■ 9. 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 repacking" 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

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

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

■ 11. 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

■ 12. 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.

■ 13. Amend § 207.20 by revising paragraph (c) to read as follows:

§ 207.20 Who must register and submit a drug list.

* * * * *

(c) Before beginning manufacture or processing of a drug subject to one of the following applications, an owner or operator of an establishment is required to register before the agency approves or grants it: A new drug

application, an abbreviated new drug application, a new animal drug application, an abbreviated new animal drug application, a medicated feed mill license application, a biologics license application, or a request for addition to the index.

* * * * *

■ 14. 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. * * *

* * * * *

■ 15. 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

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

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

■ 17. 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.

■ 18. 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.

■ 19. 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

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

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

■ 21. 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

■ 22. 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.

■ 23. 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(c)(3) 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 granting of a request for a modification, as provided for in § 516.161(b)(1) of this chapter.

* * * * *

■ 24. 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

■ 25. 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.

■ 26. 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.

* * * * *

■ 27. 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.

■ 28. 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

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

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

■ 30. Amend § 511.1 by adding 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

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

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

■ 32. 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.

* * * * *

■ 33. 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.

* * * * *

PART 516—NEW ANIMAL DRUGS FOR MINOR USE AND MINOR SPECIES

■ 34. The authority citation for part 516 is revised to read as follows:

Authority: 21 U.S.C. 360ccc–1, 360ccc–2, 371.

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

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

Sec.

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, nonfood 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 OMUMS 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 has the same meaning as that given in § 516.13 of this chapter.

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.

(c) The definitions of the following terms are given in § 516.3 of this chapter:

Same dosage form.

Same drug.

Same intended use.

§ 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, OMUMS. 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, OMUMS, 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, OMUMS, 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 60 days of the date FDA sends its notice.

(c) Within 45 days of receiving a request for an informal conference, FDA will schedule and hold the informal conference 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 scheduled meeting. Generally, this written response would be attached to 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) [Reserved]

(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. Whenever time permits, the parties to the informal conference will have 30 days to review and comment on the report.

(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 presiding officer's written report.

(4) 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 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, OMUMS.

(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, OMUMS, 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 a significant aspect of target animal safety or 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, OMUMS, 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, OMUMS, 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, OMUMS, 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 followup. 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

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

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

■ 37. 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) of the Federal Food, Drug, and Cosmetic Act (the act) or listed in the index under section 572 of 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 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.

* * * * *

■ 38. 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 Federal Food, Drug, and Cosmetic Act (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.

* * * * *

■ 39. 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

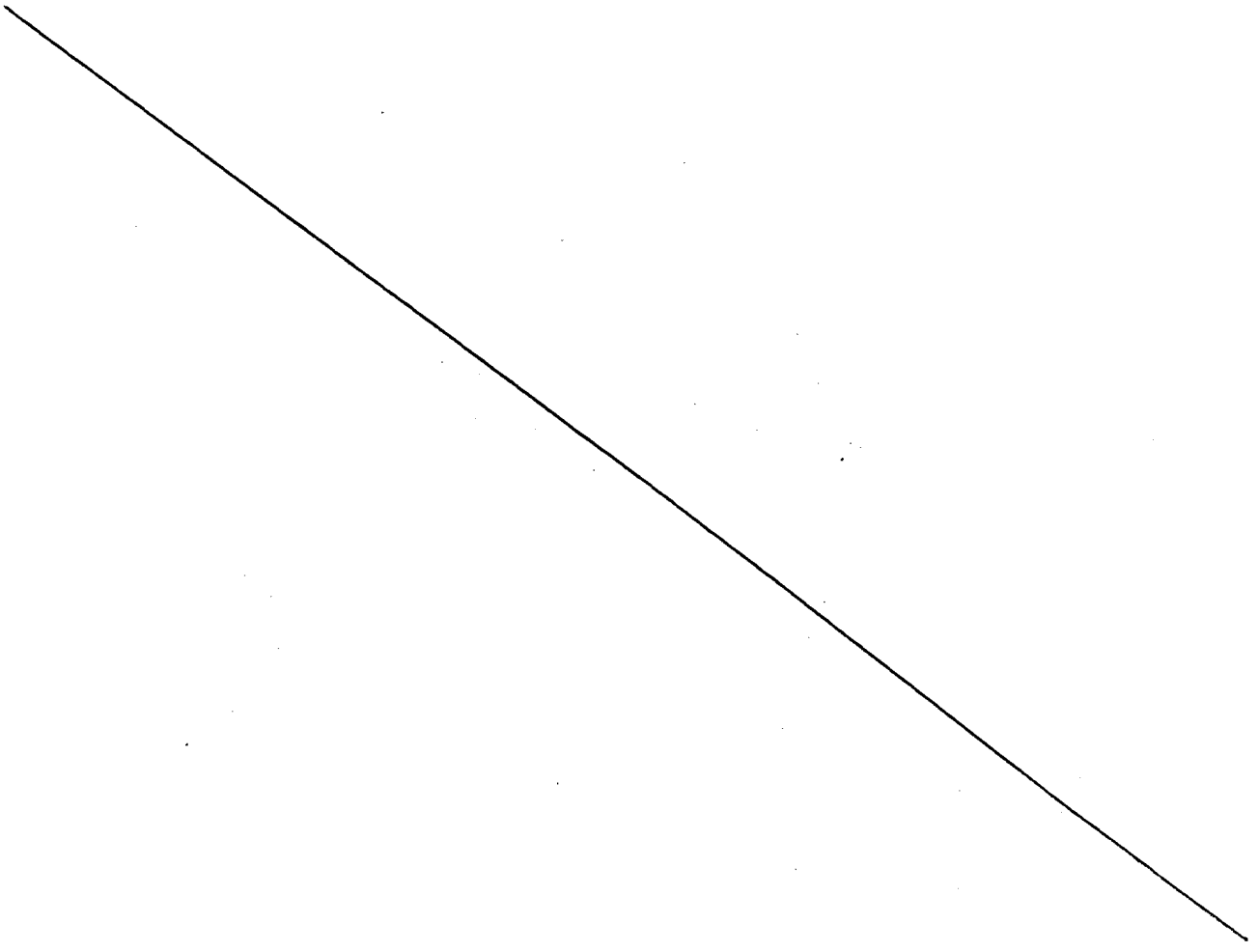
■ 40. The authority citation for 21 CFR part 589 continues to read as follows:

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

■ 41. 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



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

Dated: NOV 27 2007

November 27, 2007.

Jeffrey Shuren,
Assistant Commissioner for Policy.

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