AGL height to reflect the same altitude using MSL. Class D airspace areas are published in paragraph 5000 of FAA Order 7400.9F dated September 10, 1998, and effective September 16, 1998, which is incorporated by reference in 14 CFR 71.1. The Class D airspace area designation listed in this document would be subsequently corrected in this order.

The Direct Final Rule Procedure

The FAA anticipates that this regulation will not result in adverse or negative comment and therefore is issuing it as a direct final rule. A substantial number of previous opportunities provided to the public to comment on essentially identical actions have resulted in negligible adverse comments or objections. Unless a written adverse or negative comment or a written notice of intent to submit an adverse or negative comment is received within the comment period, the regulation will become effective on the date specified above. After the close of the comment period, the FAA will publish a document in the **Federal Register** indicating that no adverse or negative comments were received and confirming the date on which the final rule will become effective. If the FAA does receive, within the comment period, an adverse or negative comment, or written notice of intent to submit such a comment, a document withdrawing the direct final rule will be published in the **Federal Register**, and a notice of proposed rulemaking may be published with a new comment period.

Comments Invited

Although this action is in the form of a final rule and was not preceded by a notice of proposed rulemaking, comments are invited on this rule. Interested persons are invited to comment on this rule by submitting such written data, views, or arguments, as they may desire. Communications should identify the Rules Docket number and be submitted in triplicate to the address specified under the caption **ADDRESSES**. All communications received on or before the closing date for comments will be considered, and this rule may be amended or withdrawn in light of the comments received. Factual information that supports the commenter's ideas and suggestions is extremely helpful in evaluating the effectiveness of this action and determining whether additional rulemaking action would be needed.

Comments are specifically invited on the overall regulatory, economic, environmental, and energy aspects of the rule that might suggest a need to modify the rule. All comments submitted will be available, both before and after the closing date for comments, in the Rules Docket for examination by interested persons. A report that summarizes each FAA-public contact concerned with the substance of this action will be filed in the Rules Docket.

Commenters wishing the FAA to acknowledge receipt of their comments submitted in response to this rule must submit a self-addressed, stamped postcard on which the following statement is made: ''Comments to Docket No. 99–AWP–8.'' The postcard will be date stamped and returned to the commenter.

Agency Findings

The regulations adopted herein will not 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. Therefore, in accordance with Executive Order 12612, it is determined that this final rule does not have sufficient federalism implications to warrant the preparation of a Federalism Assessment.

The FAA has determined that this regulation is noncontroversial and unlikely to result in adverse or negative comments. For the reasons discussed in the preamble, this regulation only involves an established body of technical regulations for which frequent and routine amendments are necessary to keep them operationally current. Therefore, this regulation—(1) Is not a ''significant regulatory action'' under Executive order 12866; (2) is not a ''significant rule'' under DOT Regulatory Policies and Procedures (44 FR 11034; February 26, 1979); and (3) does not warrant preparation of a Regulatory Evaluation as the anticipated impact is so minimal. Since this is a routine matter that will only affect air traffic procedures and air navigation, it is certified that this rule will not have a significant economic impact on a substantial number of small entities under the criteria of the Regulatory Flexibility Act.

List of Subjects in 14 CFR Part 71

Airspace, Incorporation by reference, Navigation (air).

Adoption of the Amendment

In consideration of the foregoing, the Federal Aviation Administration amends 14 CFR part 71 as follows:

PART 71—DESIGNATION OF CLASS A, CLASS B, CLASS C, CLASS D, AND CLASS E AIRSPACE AREAS; ROUTES; AND REPORTING POINTS.

1. The authority citation for part 71 continues to read as follows:

Authority: 49 U.S.C. 106(g), 40103, 40113, 40120; E.O. 10854, 24 FR 9565, 3 CFR, 1959–1963 comp., p. 389; 14 CFR 11.69.

§ 71.1 [Correction]

2. The incorporation by reference in 14 CFR 71.1 of the Federal Aviation Administration Order 7400.9F, Airspace Designations and Reporting Points, dated September 10, 1998, and effective September 16, 1998, is amended as follows:

Paragraph 500. Class D Airspace

* * * * *

AWP AZ D Bullhead City, AZ [Correction]

Laughlin/Bullhead International Airport, AZ
(Lat. 35°09′27″ N, long. 114 °33′34″ W)

That airspace extending upward from the surface to and including 3,200 feet MSL within a 4.2-mile radius of the Laughlin/Bullhead International Airport; excluding that airspace west of a line 1.8 miles west of and parallel to the north/south runway. This Class D airspace area is effective during the specific dates and time established in advance by a Notice to Airmen. The effective date and time will thereafter be continuously published in the Airport/Facility Directory.

Issued in Los Angeles, California, on June 17, 1999.

Charles A. Ullman,

Acting Manager, Air Traffic Division, Western-Pacific Region.

[FR Doc. 99–17173 Filed 7–27–99; 8:45 am]

BILLING CODE 4910–13–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 514

[Docket No. 97N–0435]

Substantial Evidence of Effectiveness of New Animal Drugs

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA), as directed by the Animal Drug Availability Act of 1996 (ADAA), is amending its new animal drug regulations to further define the term ''substantial evidence.'' The purpose of this final rule is to encourage the submission of new animal drug applications (NADA's) and supplemental NADA's for single

ingredient and combination new animal drugs. The final rule also encourages dose range labeling.

EFFECTIVE DATE: August 27, 1999.

FOR FURTHER INFORMATION CONTACT: Herman M. Schoenemann, Center for Veterinary Medicine (HFV–126), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–827–0220.

SUPPLEMENTARY INFORMATION:

I. Background

Congress enacted the ADAA (Pub. L. 104–250) on October 9, 1996. The purpose of the ADAA is to facilitate the approval and marketing of new animal drugs and medicated feeds. In furtherance of this purpose, section 2(a) of the ADAA amended section 512(d)(3) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360b(d)(3)) to revise parts of the definition of ''substantial evidence.'' Section 2(e) of the ADAA directs FDA to issue proposed regulations and final regulations to further define ''substantial evidence'' and to encourage dose range labeling. In the **Federal Register** of November 5, 1997 (62 FR 59830), FDA proposed to amend its regulations in part 514 (21 CFR part 514) to further define ''substantial evidence'' and to encourage dose range labeling. FDA provided 90 days for public comment on the proposed rule.

Before FDA can approve a new animal drug, FDA must find, among other things, that there is substantial evidence that the new animal drug is effective for its intended uses under the conditions of use prescribed, recommended, or suggested in the proposed labeling. The changes made to the definition of ''substantial evidence'' by the ADAA and by the further definition of that term in this final rule give FDA greater flexibility to make case-specific scientific determinations regarding the number and types of adequate and well-controlled studies that will provide, in an efficient manner, substantial evidence that a new animal drug is effective.

II. Comments on the Proposed Rule

FDA received nine letters, primarily from trade associations and manufacturers, commenting on the proposed definition of ''substantial evidence.'' One comment stated a belief that the proposed definition of substantial evidence, particularly the provisions that allow FDA to exercise more flexibility in determining the most efficient and cost effective number and types of studies required and the provision that encourages dose range labeling, will benefit sponsors by reducing some costs to gain approvals of animal drugs, for both major and minor species. In general, however, the comments objected to the tone of the preamble to the proposed regulation. The comments raised specific objections to FDA's statement that a single adequate and well-controlled study frequently will not suffice to establish the effectiveness of a new animal drug, the definition of an antibacterial, and the perceived prejudice expressed by FDA against the use of published and foreign studies.

A. Substantial Evidence (§ 514.4)

1. Several comments objected to the tone of the preamble to the proposed rule. One comment noted that while the proposed language of the regulation seemingly is consistent with the flexibility envisioned by the ADAA, the preamble provides content and meaning, which appear to be inconsistent with the spirit of the ADAA and its legislative history. Specifically, the comment stated that the real focus of FDA's oversight should be to ensure that new animal drugs are safe and the effectiveness study(ies) is of sufficient quality to demonstrate substantial evidence of effectiveness. The comment alleged that the preamble departs from the notion that flexibility was intended to be utilized in a way that would minimize the burden on sponsors. The comment suggested the elimination of § 514.4(b)(3)(i) relating to the number of studies and the addition of the following sentence to proposed § 514.4(b)(3)(ii) relating to types of studies: ''Every effort will be made to require the least burdensome type of study.''

The definition of substantial evidence as revised by Congress continues to require a sponsor to submit substantial evidence of effectiveness, such that qualified experts can fairly and reasonably conclude that a new animal drug will have the effect it purports to have under the conditions of use prescribed, recommended, or suggested (hereinafter suggested) in the proposed labeling. As a comment notes, the proposed language of the regulation is consistent with the ADAA. The proposed regulation gives FDA the flexibility to make case-specific scientific determinations regarding the number and types of adequate and well-controlled studies that will provide, in an efficient manner, substantial evidence that a new animal drug is effective. It is FDA's intent to work with sponsors to identify the least burdensome appropriate means for demonstrating that a new animal drug is safe and effective. The number and types of adequate and well-controlled studies needed to demonstrate by substantial evidence that a new animal drug is effective will need to be sufficient to lead qualified experts to conclude that the new animal drug is effective. Thus, as proposed § 514.4(a) already states, ''Substantial evidence shall include such adequate and well-controlled studies that are, as a matter of sound scientific judgment, necessary to establish that a new animal drug will have its intended effect.'' Addition of the language suggested by the comment is not necessary.

In the preamble to the proposed rule, the discussion regarding the number of studies focused on two sound scientific principles: Independent substantiation and inferential value. The goal of independent substantiation is to provide adequate assurance that an experimental finding is not the result of unanticipated, undetected, systematic biases or chance. Inferential value of data relates to the confidence with which the data relating to effectiveness of a new animal drug for an intended use under the conditions tested can be used to conclude that the new animal drug will be effective in the target animal population for the intended use and associated conditions of use suggested in the proposed labeling. FDA anticipates and welcomes further discussion of implementation of the regulation. The principles of independent substantiation and inferential value form a sound scientific basis upon which these discussions can proceed.

B. Intended Uses and Conditions of Use (§ 514.4(b)(2))

2. One comment suggested that FDA introduced in its discussion of dose range labeling the concept of risk-assessment. The comment criticized FDA's failure to further explain that term and suggests that FDA is making a safety assessment within the context of the substantial evidence determination. The comment further noted that with the elimination of the requirement for dose optimization it is unclear the extent to which FDA is requesting dose response information.

Proposed § 514.4(b)(2) requires that a sponsor demonstrate that a new animal drug is effective for each proposed intended use and associated conditions of use, including the dose or dose range. Before enactment of the ADAA, FDA could not approve a new animal drug for use at a particular dose or over a dose range that exceeded the dose reasonably required to accomplish the physical or other technical effect for

which the new animal drug was intended, the optimum dose. This required that sponsors conduct adequate and well-controlled dose titration studies to characterize the critical aspects of the dose-response relationship. As part of the approval process, FDA used this information regarding effectiveness and weighed it against safety information to make a risk-benefit assessment of a new animal drug. Thus, the concept of a risk-benefit assessment is not new.

As explained in the preamble to the proposed rule, a risk-benefit assessment is a determination whether the effectiveness of a new animal drug outweighs the risks to the target animal at the dose or over the dose range prescribed in the proposed labeling. Thus, it is more accurately termed a risk-effect assessment. The application of a risk-effect assessment has always been a part of FDA's decision whether to approve a new animal drug. The risk-effect assessment is not made within the context of the substantial evidence determination but is made within the context of the approval decision.

While the ADAA modified the definition of substantial evidence and eliminated the requirement for dose titration, the other provisions of the act relating to approval of a new animal drug continue to be applicable. The act provides that FDA will refuse to approve an NADA or a supplemental NADA if, based on a fair evaluation of all material facts, the labeling for the new animal drug is false or misleading. Because before enactment of the ADAA, FDA could only approve a new animal drug at or below the optimum dose or over a dose range, the upper limit of which is at or below the optimum dose, there came to be the expectation that the dose suggested on a label is the optimum dose or that there is increasing effectiveness over the dose range suggested. Even though the requirement for dose optimization has been eliminated, there is still a need to sufficiently characterize the dose-response relationship so that the labeling is not false or misleading.

Sponsors should justify the dosage (i.e., dose or dose range, dosing frequency, and the dosing duration) and characterize for each intended use and associated conditions of use the critical aspects of the dose-response relationship relevant to the dose or dose range selected. While the sponsor must demonstrate by substantial evidence that the new animal drug is effective at the dose or over the dose range selected, the justification of the dosage and characterization of the dose-response relationship need not be demonstrated by substantial evidence. Nonetheless, a sponsor may in the interest of minimizing the number of studies conduct a single adequate and well-controlled study that both demonstrates that a new animal drug is effective at the dose or over the dose range recommended in the label and characterizes the dose-response relationship under the proposed conditions of use.

3. One comment expressed concern that FDA may use its general authority to prevent false and misleading labeling as a pretext for requiring more studies even as the definition of substantial evidence has become more flexible.

It is not FDA's intent to use the false and misleading provision to circumvent the spirit of the ADAA and require more than the number and types of studies needed by FDA to fairly and reasonably conclude that a new animal drug is effective. Nonetheless, one of the criteria for approval is that FDA find, based on a fair evaluation of all material facts, that the labeling for the new animal drug is not false or misleading (21 U.S.C. 512(d)(1)(H)). Therefore, as discussed in comment 2 of section II.B of this document, some studies may be necessary to justify the dosage and characterize the dose-response relationship so that a new animal drug can be labeled properly to inform the user about the effectiveness of the new animal drug at the suggested dose or over the suggested dose range. There may be other instances in which no additional studies are needed but FDA or the sponsor has knowledge about the effectiveness of the new animal drug that must be addressed in the labeling for the drug so that it is not false and misleading. For example, FDA or the sponsor may be aware that even though a combination new animal drug is approvable under 21 U.S.C. 512(d)(4), one active ingredient or animal drug in the combination may interfere with the effectiveness of another active ingredient or drug in the combination. In such an instance, the labeling for the combination new animal drug should indicate that the active ingredient or drug may be less effective for its intended use when used in combination than if it were applied or administered separately.

4. One comment suggested that § 514.4(b) (characteristics of substantial evidence) be revised. The comment suggested that the first word, ''Studies,'' in § 514.4(b)(1) and (b)(2) be changed to ''A study or studies.'' The comment also suggested that the sentence, ''Sponsors should, to the extent possible, provide for a dose range because it increases the utility of the new animal drug by providing the user flexibility in the selection of a safe and effective dose.'' be changed to read as follows: ''Sponsors should, at their discretion and to the extent possible, provide for a dose range because it increases the utility of the new animal drug by providing the user flexibility in the selection of a safe and effective dose.''

Because substantial evidence can consist of one or more adequate and well-controlled studies, § 514.4(b)(1) has been changed in this final rule to read ''Any study that is intended to be part of substantial evidence of the effectiveness * * *.'' Upon further consideration, FDA also has revised § 514.4(b)(2) to read as follows: ''Substantial evidence of effectiveness of a new animal drug shall demonstrate that the new animal drug is effective for each intended use and associated conditions of use for, and under, which approval is sought.'' This revision clarifies the point that proposed § 514.4(b)(2) was intended to convey, whether one study or multiple studies are submitted as substantial evidence of effectiveness, FDA must be able to determine by substantial evidence that the new animal drug is effective for each of its intended uses and conditions of use.

FDA has not changed § 514.4(b)(2)(i) to add ''at [the sponsor's] discretion and.'' Section 514.4(b)(2)(i) already states that dose range labeling should be utilized to the ''extent possible.'' Dose range labeling always is at the discretion of the sponsor. Approval of new animal drugs for use over a dose range, however, gives the users greater flexibility and, therefore, increases the utility of new animal drugs. Thus, in the spirit of the ADAA and as directed by section 2(e)(2)(C) of the ADAA, this final regulation implies sponsor discretion as well as encourages the use of dose range labeling.

FDA has revised proposed § 514.4(b)(2)(i) to clarify that this section states the requirements that generally apply to demonstrating the effectiveness of a new animal drug over a dose range and to address dose range labeling by specific intended use to make it consistent with the other provisions of the regulation. Generally, substantial evidence for a new animal drug intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease must consist of at least one adequate and well-controlled study on the basis of which qualified experts could fairly and reasonably conclude that the new animal drug will be effective for that intended use at the lowest dose of the dose range suggested in the proposed labeling for that

intended use. In many instances, there is a well-established scientific basis on which experts can conclude that effectiveness of a new animal drug, particularly those intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease caused by bacteria or other pathogenic organisms, will not decrease as the dose increases. In such instances, qualified experts can fairly and reasonably conclude that if a new animal drug is effective for an intended use at the lowest dose in the suggested dose range, the new animal drug will be effective over the entire suggested dose range for the intended use, the upper limit of which will generally be established based upon target animal safety, human food safety, or practicality. For new animal drugs intended to affect the structure or function of the body of an animal, scientific evidence does not generally exist to permit experts to conclude that the effectiveness of such a new animal drug will not decrease as the dose increases. In this case, substantial evidence to support the dose range for the intended use must consist of at least one adequate and well-controlled study on the basis of which qualified experts could fairly and reasonably conclude that the new animal drug will be effective for such intended use at all the doses within the dose range suggested on the proposed labeling. Similarly, for certain new animal drugs intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease other than that caused by bacteria or other pathogenic organisms, substantial evidence may need to consist of at least one adequate and well-controlled study on the basis of which qualified experts could fairly and reasonably conclude that the new animal drug will be effective for such intended use at all the doses within the dose range suggested on the proposed labeling. FDA intends to issue further guidance regarding the substantial evidence needed to demonstrate the effectiveness of new animal drugs over dose ranges.

C. Number of Studies (§ 514.4(b)(3)(i))

5. One comment suggested that § 514.4(b)(3)(i) (number of studies) be removed. No basis for the proposal to remove this section was provided.

Section 514.4(b)(3)(i) provides objective criteria for determining how many adequate and well-controlled studies are needed to demonstrate by substantial evidence that a new animal drug is effective for its intended uses under the conditions of use suggested in the proposed labeling. FDA believes these scientifically-based criteria provide sponsors considerable flexibility to work with FDA to design an approvable application. Therefore, FDA is not removing § 514.4(b)(3)(i). FDA is, however, changing ''an intended use'' to ''each intended use'' to make it clear that a sponsor must demonstrate that a new animal drug is effective for each proposed intended use and associated conditions of use.

6. Several comments objected to language in the preamble to the proposed rule that indicates that FDA believes that there will be limited instances in which it can rely on a single adequate and well-controlled study to determine the effectiveness of a new animal drug. Comments interpreted this language to mean that a drug sponsor's burden with respect to new animal drug development will not be lessened at all by the regulations implementing the ADAA and, therefore, believe such language is contrary to the spirit of the ADAA. The comments also referred to the discussion in the preamble that indicates that FDA is more likely to rely on a single adequate and well-controlled study if it is a multicenter study. Comments questioned the meaning of the term multicenter study. One comment urged FDA to retract the language in the preamble stating where only one study is to be accepted as substantial evidence of effectiveness, it would generally need to be a multicenter study. The comment also urged FDA to provide in the final rule and other appropriate guidance documents a detailed explanation of the underlying principles that should guide the design of a study.

When Congress made changes to the definition of substantial evidence under the ADAA, Congress did not change the standard that evidence must meet to constitute substantial evidence. The definition of substantial evidence, both before and after the ADAA, requires that the evidence provided must be such that qualified experts can fairly and reasonably conclude that the new animal drug would be effective for the intended uses and conditions of use suggested in the proposed labeling. Thus as amended by the ADAA, the act permits FDA to rely on a single adequate and well-controlled study if FDA can fairly and reasonably conclude from such a study that the new animal drug is effective. As discussed in the preamble to the proposed regulation, any study(ies) that supports a determination that a new animal drug is effective must provide independent substantiation that experimental findings of effectiveness are not the result of: unanticipated, undetected, or systematic biases or chance. As the preamble notes, independent substantiation can be achieved by conducting multiple adequate and well-controlled studies that corroborate the results of one another. However, the preamble also suggests characteristics of a single adequate and well-controlled study the presence of which can provide independent substantiation: The study involves prospective randomized stratifications or identified analytic subsets that each show a significant effect; the study includes multiple endpoints involving different events; the study provides highly reliable and statistically strong evidence of effectiveness; or the study is a multicenter study in which no single study site provides an unusually large fraction of the target animals and no single investigator or site is disproportionately responsible for the effects seen. A multicenter study is a study of a design in which a single study protocol, with allowance for minor site-specific modifications, is followed at multiple locations.

Experts must be able to fairly and reasonably conclude by substantial evidence that a new animal drug is effective for all the conditions of use prescribed, recommended or suggested in the proposed labeling. Thus, the second scientific principle enunciated in the proposed regulation is that the study(ies) that constitute substantial evidence must have sufficient inferential value. If the proposed conditions of use for a new animal drug vary widely (e.g., geographic conditions, husbandry practices, animal genetics), one adequate and well-controlled study conducted at a single location may not provide representative conditions of use from which experts can conclude that the new animal drug is effective for all of the conditions of use suggested in the proposed labeling. However, if a single adequate and well-controlled study can be designed which is representative of varied conditions of use, such a study may provide adequate inferential value upon which experts can determine whether there is substantial evidence that the drug is effective.

As FDA stated in the preamble to the proposed regulation, the number and types of studies needed to demonstrate that a new animal drug is effective will depend upon how narrowly or broadly the intended uses and conditions of use for the new animal drug are defined as well as existing knowledge about the new animal drug, similar compounds, or the disease to be treated or structure or function to be affected. It should not be assumed that a drug sponsor's burden with respect to new animal drug development will not be lessened at all

by the regulations implementing the ADAA when FDA determines that a single adequate and well-controlled study will not suffice to establish the effectiveness of a new animal drug. In addition to giving FDA greater flexibility regarding the number of studies that are needed to demonstrate that a new animal drug is effective, the ADAA eliminated the requirement for a field study in some instances and listed many types of adequate and well-controlled studies that can be submitted to support a determination by FDA that a new animal drug is effective. Whether the burden on sponsors is lessened will be a function of the types of studies as well as the number of studies conducted. FDA reiterates that it is FDA's intent to work with sponsors to identify the least burdensome appropriate means for demonstrating that a new animal drug is safe and effective.

With the further explanation given in this response, FDA does not believe it necessary to retract its statement that where only one adequate and well-controlled study is to be accepted as substantial evidence of effectiveness, that single study should provide sufficient inferential value and independent substantiation of the results of the study to permit qualified experts to determine whether the new animal drug is effective. The underlying principles that govern the design of a study intended to demonstrate effectiveness are already set forth in the further definition of adequate and well-controlled study that published in the **Federal Register** of March 5, 1998 (63 FR 10765). FDA will, subject to public input, issue further guidance on how to determine the number and types of studies necessary to demonstrate by substantial evidence that a new animal drug is effective. FDA will consider various public forums, including workshops, for discussing the number and types of studies necessary to demonstrate by substantial evidence that a new animal drug, production or therapeutic, is effective. Use of single studies as substantial evidence of the effectiveness of a new animal drug intended for production purposes, among other issues, will be further discussed in a public forum.

7. Another comment expressed concern regarding how the presumption that for one study to be accepted as substantial evidence it would generally need to be a multicenter study applies to field studies. The comment noted that the specific intent of Congress in redefining substantial evidence was to eliminate the requirement that a field study be conducted in all instances to prove effectiveness and further that FDA move away from the longstanding notion that, where one or more field investigations are required, there must be three investigations in geographically distinct regions of the country. The comment also noted that there is no meaningful difference between multiple field studies and a single field study with multiple study centers and, therefore, FDA should have to justify requesting multiple sites just as it is required to justify a requirement for more than one field study.

As discussed in comment 6 of section II.C of this document, substantial evidence is predicated on the principles of independent substantiation and inferential value to meet the statutory requirement that the studies must be sufficient such that experts can fairly and reasonably conclude the drug is effective for the intended uses and conditions of use suggested in the proposed labeling. Studies conducted at more than one site provide a basis for satisfying these criteria, but FDA will consider alternative approaches. These underlying principles apply equally to laboratory and field studies. Whether a field study is needed to demonstrate effectiveness depends upon the new animal drug and the nature of its intended uses. The legislative history of the ADAA recognized this fact. ''Assessing the safety and effectiveness of new animal drugs under conditions of use which closely approximate actual field use conditions will remain an important element of many new animal drug approvals.'' H. Rept. 104–823 at 15. However, there are situations, e.g., approval of anthelmintics, in which the effectiveness of the new animal drug can be demonstrated without a field study.

The act, as amended by the ADAA, entitles any person intending to file a request for investigational use of a new animal drug, an NADA, or a supplemental NADA to request one or more presubmission conferences. If it is decided during a presubmission conference that more than one field study is needed to demonstrate effectiveness, FDA is statutorily required to provide a written order setting forth a scientific justification for requiring more than one field study. In those instances in which FDA requires more than one field study, FDA will provide written scientific justification for such a requirement. One study can be a study at a single location or a study in which data are collected from multiple locations, and FDA agrees with the comments that the need for a multilocation field study falls within the spirit of the justification provision of the ADAA. Therefore, if FDA requires a field study to be conducted at multiple locations, FDA will provide a scientific justification for requiring the study to be conducted at multiple locations.

FDA plans to issue guidance or regulations to describe how to request a presubmission conference and to describe the procedures for the conduct of the presubmission conference. FDA also intends to issue guidance regarding the circumstances under which more than one field study may be necessary to demonstrate effectiveness. For example, FDA would require more than one field study when a single field study, although adequate and well-controlled, would not provide results from which valid inferences can be drawn regarding whether the new animal drug is effective under actual conditions of use for the intended uses suggested in the proposed labeling. In developing guidance on this issue, FDA will solicit public input.

8. Several comments criticized FDA's introduction of the terms ''persuasiveness'' and ''sufficient quality'' to describe the required characteristics of effectiveness studies. The comments noted that the statute requires that effectiveness studies be adequate and well-controlled.

Substantial evidence as defined in the act is evidence consisting of one or more adequate and well-controlled studies by experts qualified by scientific training and experience to evaluate the effectiveness of the drug, on the basis of which it could fairly and reasonably be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling. Thus, to maintain that the statute requires that effectiveness studies be adequate and well-controlled is to acknowledge only half of the statutory requirement. As stated earlier in this preamble, Congress did not change the standard that evidence must meet to be substantial evidence. Not only must the study(ies) that constitute substantial evidence be adequate and well-controlled, the study(ies) must also provide a basis upon which qualified experts can fairly and reasonably conclude that a new animal drug is effective.

FDA has by regulation further defined the characteristics of adequate and well-controlled studies (63 FR 10765); these characteristics relate primarily to the design of an adequate and well-controlled study. The terms ''sufficient quality'' and ''persuasiveness'' relate respectively to the conduct and results of the study.

The fact that a study is an adequate and well-controlled study does not mean that the results of such a study will support a finding that a new animal drug is effective. Whether experts can reasonably conclude from adequate and well-controlled studies that a new animal drug is effective will depend upon the quality of the studies, i.e., whether the study was actually conducted in accordance with the study design as described in the study protocol and in accordance with reasonable scientific practices for the conduct of studies. Whether experts can conclude that a new animal drug is effective will further depend upon whether the results of adequate and well-controlled studies persuade experts that the new animal drug is effective for its intended uses under the conditions of use suggested in the proposed labeling. Results of a study are likely to be persuasive if the parameters selected for measurement and the measured responses reliably reflect the effectiveness of the new animal drug, the results are likely to be repeatable, and valid inferences can be drawn to the target animal population.

Persuasiveness and sufficient quality are adjectives that describe those adequate and well-controlled studies that will lead qualified experts to conclude that a new animal drug is effective. Thus, § 514.4(b)(3)(i) continues to include reference to those terms.

9. Another comment asserted that effectiveness need not be demonstrated for all conceivable variations of genetic and environmental conditions because it is the intent of the ADAA to encourage the submission of NADA's and supplemental NADA's.

The purpose of the ADAA was to build needed flexibility into FDA's animal drug review processes to enable more efficient approval and more expeditious marketing of safe and effective animal drugs. The ADAA did not eliminate the requirement that sponsors demonstrate that a new animal drug has the effect it purports or is represented to have under the conditions of use suggested in the proposed labeling. FDA agrees that substantial evidence need not consist of a direct demonstration that a new animal drug is effective under all conceivable genetic and environmental conditions. However, a sponsor does need to demonstrate that a new animal drug is effective under genetic and environmental conditions sufficiently representative of the conditions of use suggested in the proposed labeling so that qualified experts can fairly and reasonably conclude that the new animal drug will be effective under those proposed conditions of use. If experts cannot so conclude, the evidence does not meet the statutory definition of substantial evidence.

10. One comment opposed FDA's proposal to consider how time may affect the inferential value of a particular set of data citing the fact that currently approved animal drugs in wide use today were approved on what could now be considered ''aged data.'' Another comment questioned how FDA will evaluate whether data are sufficiently ''current'' for purposes of submitting an NADA.

Approval decisions are made at a specific point in time and FDA must be able to fairly and reasonably conclude from the data available at the time it makes its approval decision whether the new animal drug is effective. The act does, however, provide that if on the basis of new information, evaluated together with the evidence available at the time the application was approved there is a lack of substantial evidence that a new animal drug is effective, FDA must take steps to withdraw the approval. Therefore, the currency of data is relevant even with respect to approved new animal drugs.

FDA only stated that time may affect the inferential value of data. FDA recognizes that not all data are equally sensitive to time. FDA will need to make determinations regarding the currency of data on a case-by-case basis. FDA agrees with the comment that the test is whether the data provide a basis on which qualified experts could fairly and reasonably conclude that the new animal drug is effective. Currency is particularly meaningful in terms of the inferences that can be drawn from data. Therefore, there may be instances in which the age of the data limit or invalidate the usefulness of data in determining the effectiveness of a new animal drug just as the discovery of new data may give FDA reason to consider withdrawing an approval.

11. One comment objected to any intent of FDA to require a demonstration of effectiveness in multiple geographic locations or under multiple management practices.

As stated previously, the act provides that in order to meet the definition of substantial evidence, the evidence provided must be such that qualified experts can fairly and reasonably conclude that the new animal drug is effective for its intended uses under the conditions of use suggested in the proposed labeling. While a sponsor generally need not demonstrate effectiveness under every condition of use suggested in the proposed labeling, a sponsor will need to demonstrate that the new animal drug is effective under conditions such that FDA will be able to fairly and reasonably conclude that the new animal drug will be effective for its intended uses under the conditions of use suggested in the proposed labeling. If a single adequate and well-controlled study can be designed, which is representative of varied conditions of use, such as varied geographic conditions and management practices, such a study would provide adequate inferential value such that experts can fairly and reasonably conclude that the drug will be effective. FDA will develop guidance on this issue, soliciting public input, and will discuss this issue on a case-by-case basis with a sponsor during a presubmission conference.

12. One comment asserted that while effectiveness must be demonstrated for each intended use, substantial evidence should not require conducting studies in every conceivable subdivision of species of animals.

FDA agrees. Adequate and well-controlled studies need only be conducted in species and subspecies that are representative of the species for which the new animal drug is intended such that qualified experts can fairly and reasonably conclude by that the new animal drug is effective for its intended uses under the conditions of use suggested in the proposed labeling. It is reasonable to expect that studies in many different subspecies or breeds will not be needed if there is a scientific basis to conclude that there will be no difference in response or safety between subspecies or breeds respectively.

D. Types of Studies (§ 514.4(b)(3)(ii))

13. Comments strongly disagreed with FDA's comments in the preamble regarding the value of published studies, peer-reviewed studies, and foreign studies. Comments asserted that such studies are useful and that the preamble to the proposed rule reflects prejudice against the use of such studies as a basis of establishing efficacy. One comment acknowledged that there may be differences in animal genetics and husbandry represented in foreign studies that may justify FDA's requiring that foreign data be confirmed but also notes that such differences may have no impact on animals' response to a drug. Another comment suggested that FDA establish guidance relating to each of these types of studies.

In the preamble to the proposed regulation, FDA clearly stated that a published study, foreign study, or a study using a model may provide substantial evidence of effectiveness if it is an adequate and well-controlled

study. Nonetheless, the utility of published studies, foreign studies, and studies using models, like studies conducted by or on behalf of sponsors, may vary because of the nature of the study. It was FDA's intent to provide in the preamble direction regarding the use of published studies, foreign studies, and studies using models.

With regard to foreign studies, the preamble noted that differences such as animal breeds, genetic composition within a breed, diseases, nutrition, and husbandry practices need to be addressed sufficiently. FDA did not preclude the use of foreign studies. Furthermore, FDA agrees that where these differences have no impact on an animal's response to a new animal drug, adequate and well-controlled foreign studies may support a finding by substantial evidence that a new animal drug is effective. FDA is willing and available to discuss with sponsors what information, if any, relating to foreign data is needed to address these kinds of differences. FDA anticipates issuing, subject to public input, guidance regarding this issue as expeditiously as resources permit.

14. One comment questioned why sponsors must disclose the source of funding for published studies asserting that the source of funding is irrelevant to the evaluation of the study.

FDA disagrees with the assertion that the source of funding is irrelevant to the evaluation of a published study. Knowledge regarding the funding of the study allows FDA to determine whether a sponsor owns, and can provide FDA access to, the study protocol, study documentation, and study data for purposes of evaluating the study. Additionally, if current and/or future funding depend upon the outcome of the study, there is a potential for bias and FDA will want to have available the study protocol, study documentation, and study data to scrutinize more closely.

Who funds the study and their purpose in sponsoring the study are also relevant because it may affect which studies are ultimately published with the result that published studies may represent a skewed subset of available information. That is, if a sponsor funds a study that supports their research, the sponsor may attempt to get the study published. But, if the study does not support their research, the sponsor may not pursue publication of the study. Thus, a search of the published literature may not accurately reflect the body of knowledge that actually exists.

15. One comment suggested that the definition of combination drugs should acknowledge that some combination drugs may be topical antibacterials which, under aquaculture conditions, might be applied in the water in which fish are raised.

Increasingly there are concerns that overuse or improper use of antibacterials may contribute unnecessarily to the development of antibacterial resistance. It is for this reason that the ADAA requires that applicants establish that nontopical antibacterials contribute to the effectiveness of a combination new animal drug. When used in aquaculture, antibacterials are applied or administered not ''topically'' in the sense that they are applied or administered to individual fish but they are applied or administered in a body of water through which fish swim. Because of the nature of the products and because of the added potential for the development and transfer of resistance in the bodies of water in which antibacterials are applied, FDA will for purposes of the application of § 514.4(c) consider aquaculture drugs administered in water to be nontopical antibacterials.

FDA has worked with the aquaculture industry to facilitate the approval of new animal drugs for use in aquaculture and recognizes that there is a vital need for the approval of more aquaculture drugs. FDA anticipates that proposals being made to facilitate the approval of new animal drugs intended for minor uses or use in minor species will provide additional tools to facilitate the approval of new animal drugs for use in aquaculture.

16. Comments relating to substantial evidence for combination drugs focused primarily on the definition of ''antibacterial.'' The comments claimed that by defining ''antibacterial'' in a way that includes classes of drugs such as anticoccidials, ionophores, and arsenicals, FDA has rendered the streamlined approval provision for certain combination drugs meaningless. The comments stated that the intent of the streamlined combination approval provision was to speed up approval of feed use combination drugs and virtually all of the economically and medicinally important combinations of drugs for food animal feeds involve an ionophore and/or arsenical and an antibacterial. Therefore, the comments urged FDA to define ''antibacterial'' in a way that ensures the exemption of anticoccidials, ionophores, and arsenicals. One comment suggested that FDA can accomplish this by exempting from the definition of ''antibacterial'' any drug use which: (1) Has been determined by FDA to have met the criteria of § 558.15 (21 CFR 558.15), or (2) was exempted by FDA from compliance with § 558.15. The comment asserted that the term ''antibacterial'' should not include chemicals that have some antibiotic activity but which are not known or speculated to contribute to the development of resistance by bacterial pathogens to antibiotics in human medicine. Another comment attempted to provide justification for excluding the ionophore class of animal drugs from the general classification of ''antibacterial'' claiming ionophores are unlikely to contribute to the development of antibacterial resistance of importance to human or veterinary medicine.

The combination new animal drug provision of section 512(d)(4) the act, added by the ADAA treats antibacterial ingredients and drugs differently from other active ingredients and animal drugs intended for use in combination because increasingly there are concerns that overuse or improper use may contribute unnecessarily to the development of antibacterial resistance. The term antibacterial does not include any new animal drug that is intended for use only to kill or suppress organisms other than bacteria. For example, the term antibacterial does not include a new animal drug which is intended to kill or suppress coccidia unless such animal drug also has an approved use in the particular species that is attributable to its antibacterial properties. Therefore, new animal drugs approved solely as anticoccidials will not fall within the definition of antibacterial.

As enacted, the ADAA did not address how specific classes of animal drugs such as arsenicals and ionophores should fit within the term antibacterial. Drugs that achieve their effect by killing or suppressing the replication of bacteria are considered to be antibacterials. If an active ingredient or animal drug intended for use in combination can be shown to act through some other mechanism to achieve its intended effect in a particular species it will not be considered an antibacterial.

On October 21, 1998, Congress, as part of the agriculture appropriations in Pub. L. 105–277, amended the act to exclude ionophores and arsenicals from the definition of antibacterial for purposes of determining whether combination new animal drugs intended for use in drinking water or animal feed qualify for the modified combination drug approval process set forth in 21 U.S.C. 512(d)(4). Therefore, FDA is revising proposed § 514.4(c)(1)(ii), final 21 CFR 514.4(c)(1)(iii), to add at the end the following: ''But, antibacterial does

not include ionophores or arsenicals intended for use in combination in animal feed or drinking water.''

17. Comments objected to the requirement in the proposed regulation that conditions treated by a combination new animal drug occur simultaneously with sufficient frequency in the intended target animal population. The comments argue that the objective of the ADAA is drug availability and, therefore, the frequency of conditions should not be considered. One comment suggested that drugs or active ingredients to be used in combination should be approved as long as there is credible medical evidence that the conditions to be treated do occur simultaneously.

As the comment suggests, the important principle that needs to be met in determining whether there is appropriate concurrent use is that there be evidence that any conditions to be treated or physiological effects intended to be achieved can occur simultaneously. Thus, FDA will find that appropriate concurrent use exists if there is credible evidence that the conditions for which the combination is intended can occur simultaneously. FDA has added a definition of appropriate concurrent use at § 514.4(c)(1)(iv) of these final rules. Because combination new animal drugs may contain animal drugs intended for therapeutic and/or production use, the definition does not adopt the comment's suggestion that there be credible ''medical'' evidence.

18. Comments objected to the provision in the proposed regulation that requires that sponsors demonstrate bioavailability as a mechanism to determine the physical compatibility and the compatibility of dosing regimens of separately approved animal drugs when used in combination. Comments assert that the ADAA clearly places the burden on FDA to make a scientifically based initial conclusion that there is reason to believe that incompatibility exists, rather than for sponsors to continue to demonstrate compatibility.

FDA has reconsidered the statutory basis for the proposed requirement that applicants demonstrate comparable bioavailability for some classes of combination new animal drugs. FDA agrees that bioavailability and compatibility are not completely correlative. However, just as the requirement to demonstrate compatibility is a recognition that under some circumstances use of an active ingredient or animal drug in a combination new animal drug may affect the effectiveness of that (or another) active ingredient or animal drug, the proposed requirement to demonstrate comparable bioavailability is a recognition that under some circumstances use of an active ingredient or animal drug in a combination new animal drug may affect the safety of that (or another) active ingredient or animal drug. Furthermore, the ADAA recognizes that this concern varies by class of combination new animal drug with dosage form new animal drugs, other than for use in drinking water, having the greatest potential to affect the effectiveness of the new animal drugs being combined, and animal drugs for use in feed having the least (see 21 U.S.C. 360b(d)(4)(C) and (d)(4)(D)). FDA believes similarly that combining dosage form new animal drugs, other than for use in drinking water, has the greatest potential to affect the safety of the new animal drugs being combined because many of these dosage form new animal drugs are indicated for serious or life-threatening conditions, have relatively narrow margins of safety, and/or have complex formulations.

Under the act, FDA may refuse to approve a combination new animal drug if there is a substantiated scientific issue specific to one or more of the animal drugs in the combination that cannot adequately be evaluated based on information in the application for the combination or there is a scientific issue raised by target animal observations contained in studies submitted to FDA as part of the application for the combination (21 U.S.C. 360b(d)(4)(B)). It is a well-accepted scientific principle that changes in formulation can affect the bioavailability and, thus, the safety and effectiveness of a new animal drug. FDA currently requires a demonstration of comparable bioavailability when a sponsor proposes to make significant formulation changes to a single active ingredient new animal drug and when a sponsor proposes to market a generic formulation of a new animal drug. In the latter case, comparable bioavailability is more formally defined as bioequivalence. Formulation changes necessitated by combining dosage form new animal drugs other than those intended for use in drinking water are considered to be significant changes that may similarly affect bioavailability and, thus, the safety of a combination new animal drug. Thus, FDA believes it is appropriate and in keeping with the spirit of the ADAA for FDA to determine that in the specific case of dosage form animal drugs intended for use in combination other than in drinking water there is a substantiated scientific issue relating to the formulation changes necessitated to combine such animal drugs that warrants the requirement for additional target animal safety data. FDA plans to issue a guidance or regulations setting forth further discussion on this issue.

Because the proposed requirement to demonstrate comparable bioavailability relates primarily to safety, FDA is eliminating proposed § 514.4(c)(2)(iv) and (c)(2)(v). New § 514.4(c)(2)(i)(C) and (c)(2)(ii)(D) will reflect that as part of demonstrating the effectiveness of certain combination new animal drugs, sponsors need only demonstrate that active ingredients or animal drugs intended for use in combination are physically compatible and/or do not have disparate dosing regimens where FDA, based on scientific information, has reason to believe there is a lack of physical compatibility or the dosing regimens are disparate.

19. One comment interpreted the preamble to the proposed regulation to require that entirely new studies with a combination new animal drug be conducted when an additional claim is added to a previously separately approved individual active ingredient or animal drug that is part of the combination new animal drug. The comment opposed such a requirement and suggested that label extensions for the combination new animal drug should be pursued at the discretion of the sponsor.

When an additional claim is approved for a single ingredient new animal drug that is part of a combination new animal drug that has been approved under the modified combination approval process provided by section 512(d)(4) of the act, the additional claim may not automatically become a claim for the combination new animal drug. A supplemental application may need to be submitted for the combination new animal drug. Otherwise, an applicant could attempt to circumvent effectiveness requirements for a combination new animal drug that qualifies for approval under the modified combination approval process by choosing to seek approval of certain claims for one of the single ingredient new animal drugs after the combination new animal drug containing it has been approved.

For example, assume that drug A is approved for indication X and drug B is approved for indication Y, and the combination new animal drug containing drug A and drug B qualifies for approval under the modified combination approval process. Because each new animal drug is intended for at least one use that is different from the

other new animal drug in the combination, the application for the combination new animal drug would primarily need to include a demonstration that combination new animal drug AB represents appropriate concurrent use to establish that the combination is effective. If drug A had been approved for indications X and Y, the application would have had to include a demonstration that drug B contributed to the labeled effectiveness of the combination new animal drug with respect to indication Y. Therefore, if drug A is subsequently approved for indication Y after the combination new animal drug AB is approved, a supplemental application is needed to demonstrate that drug B contributes to the labeled effectiveness of the combination new animal drug. In no case will FDA require any more than FDA would have required had the applicant originally sought approval of a combination new animal drug that includes the animal drug with the additional claim.

20. One comment requested confirmation regarding the application of the combination new animal drug provision of the proposed regulation. In particular, the comment sought confirmation that sponsors need only show that each antibacterial in a combination new animal drug makes a contribution to a combination's effectiveness. The comment further sought confirmation that the contribution of nonantibacterials that have no overlapping claims need not be demonstrated.

Section 514.3(c) specifies the requirements for demonstrating that a combination new animal drug is effective. Because increasingly there are concerns that overuse or improper use of antibacterials may contribute unnecessarily to the development of antibacterial resistance, there are additional, specific requirements that relate to combination new animal drugs that contain antibacterial ingredients or animal drugs.

For those combinations that contain antibacterials and qualify for the modified combination approval process provided under section 512(d) of the act, a sponsor will need to show more than that each antibacterial makes a contribution to the combination's effectiveness. The sponsor will also have to demonstrate: (1) That each nonantibacterial active ingredient or animal drug that is intended only for the same use as another active ingredient or animal drug makes a contribution to effectiveness and (2) each antibacterial and nonantibacterial active ingredient or animal drug with a unique claim provides appropriate concurrent use. Furthermore, the sponsor may, under certain circumstances, need to demonstrate that the active ingredients or animal drugs are physically compatible and/or do not have disparate dosing regimens.

If each of the active ingredients or animal drugs intended for use in a combination that qualifies for the modified approval process has a unique claim, the sponsor must demonstrate that each active ingredient or animal drug provides appropriate concurrent use. The sponsor may, under certain circumstances, also need to demonstrate that the active ingredients or animal drugs are physically compatible and/or do not have disparate dosing regimens.

21. One comment criticized the length and complexity of proposed § 514.4(c)(2), which describes the substantial evidence required for the evaluation of combination new animal drugs with active ingredients or animal drugs that have previously been separately approved.

FDA has made some revisions to proposed § 514.4(c)(2) in an attempt to make the provision more understandable. Unfortunately the combination new animal drug provision of the act, section 512(d)(4), is complex. One of the revisions includes defining ''dosage form combination new animal drug'' at § 514.4(c)(1)(ii). FDA has also tried to simplify the provision, by describing in list form for dosage form combination new animal drugs and combination new animal drugs intended for use in animal feed or drinking water separately, what substantial evidence is needed to demonstrate that a combination of previously separately approved active ingredients or animal drugs is effective. The preamble to the proposed rule provides further explanation of the substantial evidence needed to demonstrate that a combination new animal drug is effective. FDA intends to issue guidance to further assist sponsors and interested parties in interpreting this very complex provision.

E. Responses to Remaining Comments

22. One comment urged FDA to make animal testing illegal.

The act requires that manufacturers of new animal drugs demonstrate prior to marketing that a new animal drug is safe to the animals administered the drug, safe to humans who may consume food derived from animals administered the drug, and effective. This final rule describes the numbers and types of studies needed to demonstrate that a new animal drug is effective. Depending upon the nature of the intended uses, which may include the alleviation of animal pain and suffering, and conditions of use of the new animal drug, substantial evidence of effectiveness may consist of one or more studies in the target animal, studies in laboratory animals, field studies, bioequivalence studies, or in vitro studies.

As stated repeatedly, FDA intends to work with sponsors to identify the least burdensome appropriate means for demonstrating that a new animal drug is safe and effective. With technological advances, the use of animals in testing has been in decline and FDA fully supports the use of alternative methodologies where appropriate. FDA balances the need for live animal testing of new animal drugs with the need to protect the welfare of the animals that would receive the new animal drug if it is approved. To the extent animal testing is used, there are in effect laws and regulations that provide for the humane care and use of animals in research, testing, and teaching environments. FDA advocates full observance of all applicable animal welfare laws, regulations, and guidelines.

23. Several comments referred to the efforts of the Center for Veterinary Medicine's ADAA Minor Use/Minor Species Working Group to propose regulatory and statutory changes to facilitate the approval of new animal drugs for minor uses or for use in minor species.

Section 2(f) of the ADAA required the Secretary of Health and Human Services to consider and announce legislative and regulatory options for facilitating the approval under section 512 of the act of animal drugs intended for minor species and for minor uses. Although the redefinition of substantial evidence by the ADAA and FDA's further definition of substantial evidence may have the indirect effect of facilitating approval of animal drugs intended for minor species and for minor uses, the charge from Congress to announce proposals for regulatory and statutory changes was not specifically addressed by FDA in redefining substantial evidence. Comments relating to proposals for facilitating the approval of animal drugs for minor use or minor species were addressed in the context of FDA's proposal for regulatory and statutory changes (63 FR 58056, October 29, 1998).

III. Conforming Changes

FDA has made conforming changes to §§ 514.1(b)(8) and 514.111.

IV. Environmental Impact

FDA has carefully considered the potential environmental impacts of this final rule. The agency has determined that this action is of a type that does not individually or cumulatively have a significant effect on the human environment (21 CFR 25.30(h)). Therefore, neither an environmental assessment nor an environmental impact statement is required.

V. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612). 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; distributive impacts; and equity). The agency believes that this final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. The Office of Management and Budget (OMB) has determined that this final rule is a significant regulatory action subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities unless the rule is not expected to have a significant impact on a substantial number of small entities. Because this final rule will not impose significant new costs on any firms, under the Regulatory Flexibility Act (5 U.S.C. 605(b)), the agency certifies that the final rule will not have a significant impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

FDA, as directed by the ADAA, is further defining ''substantial evidence,'' the standard by which a new animal drug is determined to be effective for its intended uses under the conditions of use represented in its labeling. The purpose of the final rule is to encourage the submission of NADA's, the submission of supplemental NADA's, and the use of dose range labeling. Accordingly, the final definition of substantial evidence, while not changing the standard of effectiveness, recognizes that ''substantial evidence,'' as redefined under the ADAA, gives FDA greater flexibility to determine the number and types of studies that adequately demonstrate the effectiveness of any particular new animal drug. For example, under the new definition, sponsor companies are no longer required, in every instance, to submit a field study to establish the effectiveness of a new animal drug under investigation. Because the new definition gives FDA greater flexibility to work with sponsors to tailor the evidence needed to demonstrate effectiveness, this final rule is not expected to impose any new costs on the industry. Furthermore, because sponsors will have more options under this revised definition to design and conduct studies to demonstrate effectiveness, and because sponsors can be expected to choose the most efficient and cost effective option, the net effect of this provision will be a benefit to sponsors.

The final rule also applies to the submission and review of NADA's for new animal drugs intended for use over a dose range. The ADAA eliminated the statutory requirement to limit the use of a new animal drug to an amount no greater than that reasonably required to accomplish the physical or other technical effect of the drug for its intended use. The act, as amended by the ADAA, permits the use of a new animal drug at any level that is safe for the target animal, effective, and will not result in a residue of such drug in excess of a tolerance found to be safe. Because dose optimization will no longer be required, sponsors are no longer required to conduct adequate and well-controlled in vivo dose titration studies, but will need only to conduct such studies as may be needed to justify the dosage and characterize the critical aspects of the dose-response relationship relevant to the dose or dose range selected so that FDA can make a risk-effect assessment and ensure that the labeling for a new animal drug is not false or misleading. Because there will be greater flexibility in determining the studies needed to justify dosage and characterize the dose-response relationship, sponsors will realize a small cost savings.

Finally, the final rule further defines substantial evidence as it relates to combination new animal drugs. For certain combination new animal drugs that contain active ingredients or animal drugs that have previously been separately approved, sponsors will not be required to conduct additional studies to demonstrate that the combination new animal drug is effective. These changes will provide further cost savings to the sponsors of NADA's that meet the criteria for the streamlined approval process. Based on comments to the proposal, FDA has reconsidered and subsequently removed the requirement in this provision that would have required applicants to demonstrate comparable bioavailability as a mechanism for determining the physical compatibility and compatibility of dosing regimens of active ingredients or animal drugs intended for use in combination.

VI. Unfunded Mandates Act of 1995

The Unfunded Mandates Act of 1995 (2 U.S.C. 1532) requires that agencies prepare an assessment of the anticipated costs and benefits before proposing any rule that may result in expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million or more (adjusted annually for inflation) in any one year. This final rule does not impose any mandates on State, local, or tribal governments, or the private sector that will result in an expenditure of $100 million or more in any one year.

VII. Paperwork Reduction Act of 1995

This final rule contains information collection provisions that are subject to review by OMB under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). A description of these provisions is given below. 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: Substantial Evidence of Effectiveness of New Animal Drugs.

Description: As directed by the ADAA, FDA is publishing a final rule to further define substantial evidence in a manner that encourages the submission of NADA's and supplemental NADA's and encourages dose range labeling. The final regulation implements the definition of ''substantial evidence'' in 21 U.S.C. 360b(d)(3) as amended by the ADAA. Substantial evidence is the standard that a sponsor must meet to demonstrate the effectiveness of a new animal drug for its intended uses under the conditions of use suggested in its proposed labeling. The final regulation, § 514.4, gives FDA greater flexibility to make case-specific scientific determinations regarding the number and types of adequate and well-controlled studies that will provide, in an efficient manner, substantial evidence that a new animal drug is effective. FDA estimated that the proposed regulation would reduce by approximately 10 percent the total annual burden associated with demonstrating the effectiveness of a new animal drug as part of an NADA or supplemental NADA submission.

Description of Respondents: Persons and businesses, including small businesses. In the **Federal Register** of November 5, 1997 (62 FR 59830), FDA requested comments on the proposed collection of information annual reporting burden estimate. As a result of comments received on the proposed regulation (see comment 18 in section II.D of this document), the requirement in the proposed regulation that sponsors demonstrate comparable bioavailability as a mechanism to determine the physical compatibility and the compatibility of dosing regimens of separately approved animal drugs intended for use in a dosage form combination new animal drug has been eliminated in the final rule. The final rule reflects that as part of demonstrating effectiveness of certain combination new animal drugs sponsors need only demonstrate that active ingredients or animal drugs intended for use in combination are physically compatible and/or do not have disparate dosing regimens where FDA, based on scientific information, has reason to believe there is a lack of physical compatibility or the dosing regimens are disparate. Because combinations that qualify for the modified approval process created by the ADAA represent a small portion of all NADA's and supplemental NADA's submitted to FDA and the majority of combinations that qualify for the modified approval process are expected to be combinations intended for use in animal feed, any reduction in paperwork burden resulting from the elimination of the requirement to demonstrate comparable bioavailability would be negligible. Therefore, FDA believes that the annual reporting burden estimate of 544,036 hours should remain unchanged.

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
514.4(a)	190	4.5	860	632.6	544,036

[1] There are no capital costs or operating and maintenance costs associated with this collection.

Individuals and organizations may submit comments on this burden estimate or on any other aspect of these information collection provisions, including suggestions for reducing the burden, and should direct them to Herman M. Schoenemann, Center for Veterinary Medicine (HFV-126), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855.

The information collection provisions in this final rule have been approved under OMB control number 0910–0356. This approval expires December 31, 2000. An agency may not conduct or sponsor, and a person is not required to provide, a collection of information unless it displays a currently valid OMB control number.

List of Subjects in 21 CFR part 514

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

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 514 is amended as follows:

PART 514—NEW ANIMAL DRUG APPLICATIONS

1. The authority citation for 21 CFR part 514 continues to read as follows:

Authority: 21 U.S.C. 351, 352, 360b, 371, 379e, 381.

2. Section 514.1 is amended by revising paragraphs (b)(8)(ii) and (b)(8)(v) to read as follows:

§ 514.1 Applications.

* * * * *

(b) * * *

(8) * * *

(ii) An application may be refused unless it includes substantial evidence of the effectiveness of the new animal drug as defined in § 514.4.

* * * * *

(v) If the new animal drug is a combination of active ingredients or animal drugs, an application may be refused unless it includes substantial evidence of the effectiveness of the combination new animal drug as required in § 514.4.

* * * * *

3. Section 514.4 is added to subpart A to read as follows:

§ 514.4 Substantial evidence.

(a) *Definition of substantial evidence.* Substantial evidence means evidence consisting of one or more adequate and well-controlled studies, such as a study in a target species, study in laboratory animals, field study, bioequivalence study, or an in vitro study, on the basis of which it could fairly and reasonably be concluded by experts qualified by scientific training and experience to evaluate the effectiveness of the new animal drug involved that the new animal drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. Substantial evidence shall include such adequate and well-controlled studies that are, as a matter of sound scientific judgment, necessary to establish that a new animal drug will have its intended effect.

(b) *Characteristics of substantial evidence*—(1) *Qualifications of experts.* Any study that is intended to be part of substantial evidence of the effectiveness of a new animal drug shall be conducted by experts qualified by scientific training and experience.

(2) *Intended uses and conditions of use.* Substantial evidence of effectiveness of a new animal drug shall demonstrate that the new animal drug is effective for each intended use and associated conditions of use for and under which approval is sought.

(i) *Dose range labeling.* Sponsors should, to the extent possible, provide for a dose range because it increases the utility of the new animal drug by providing the user flexibility in the selection of a safe and effective dose. In general, substantial evidence to support dose range labeling for a new animal drug intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease must consist of at least one adequate and well-controlled study on the basis of which qualified experts could fairly and reasonably conclude that the new animal drug will be effective for the intended use at the lowest dose of the dose range suggested in the proposed labeling for that intended use. Substantial evidence to support dose range labeling for a new animal drug intended to affect the structure or function of the body of an animal generally must consist of at least one adequate and well-controlled study on the basis of which qualified experts could fairly and reasonably conclude

that the new animal drug will be effective for the intended use at all doses within the range suggested in the proposed labeling for the intended use.

(ii) [Reserved]

(3) *Studies*—(i) *Number.* Substantial evidence of the effectiveness of a new animal drug for each intended use and associated conditions of use shall consist of a sufficient number of current adequate and well-controlled studies of sufficient quality and persuasiveness to permit qualified experts:

(A) To determine that the parameters selected for measurement and the measured responses reliably reflect the effectiveness of the new animal drug;

(B) To determine that the results obtained are likely to be repeatable, and that valid inferences can be drawn to the target animal population; and

(C) To conclude that the new animal drug is effective for the intended use at the dose or dose range and associated conditions of use prescribed, recommended, or suggested in the proposed labeling.

(ii) *Types.* Adequate and well-controlled studies that are intended to provide substantial evidence of the effectiveness of a new animal drug may include, but are not limited to, published studies, foreign studies, studies using models, and studies conducted by or on behalf of the sponsor. Studies using models shall be validated to establish an adequate relationship of parameters measured and effects observed in the model with one or more significant effects of treatment.

(c) *Substantial evidence for combination new animal drugs*—(1) *Definitions.* The following definitions of terms apply to this section:

(i) *Combination new animal drug* means a new animal drug that contains more than one active ingredient or animal drug that is applied or administered simultaneously in a single dosage form or simultaneously in or on animal feed or drinking water.

(ii) *Dosage form combination new animal drug* means a combination new animal drug intended for use other than in animal feed or drinking water.

(iii) *Antibacterial* with respect to a particular target animal species means an active ingredient or animal drug: That is approved in that species for the diagnosis, cure, mitigation, treatment, or prevention of bacterial disease; or that is approved for use in that species for any other use that is attributable to its antibacterial properties. But, antibacterial does not include ionophores or arsenicals intended for use in combination in animal feed or drinking water.

(iv) *Appropriate concurrent use* exists when there is credible evidence that the conditions for which the combination new animal drug is intended can occur simultaneously.

(2) *Combination new animal drugs that contain only active ingredients or animal drugs that have previously been separately approved.*

(i) For dosage form combination new animal drugs, except for those that contain a nontopical antibacterial, that contain only active ingredients or animal drugs that have previously been separately approved for the particular uses and conditions of use for which they are intended in combination, a sponsor shall demonstrate:

(A) By substantial evidence, as defined in this section, that any active ingredient or animal drug intended only for the same use as another active ingredient or animal drug in the combination makes a contribution to the effectiveness of the combination new animal drug;

(B) That each active ingredient or animal drug intended for at least one use that is different from all the other active ingredients or animal drugs used in the combination provides appropriate concurrent use for the intended target animal population; and

(C) That the active ingredients or animal drugs are physically compatible and do not have disparate dosing regimens if FDA, based on scientific information, has reason to believe the active ingredients or animal drugs are physically incompatible or have disparate dosing regimens.

(ii) For combination new animal drugs intended for use in animal feed or drinking water that contain only active ingredients or animal drugs that have previously been separately approved for the particular uses and conditions of use for which they are intended in combination, the sponsor shall demonstrate:

(A) By substantial evidence, as defined in this section, that any active ingredient or animal drug intended only for the same use as another active ingredient or animal drug in the combination makes a contribution to the effectiveness of the combination new animal drug;

(B) For such combination new animal drugs that contain more than one antibacterial ingredient or animal drug, by substantial evidence, as defined in this section, that each antibacterial makes a contribution to labeled effectiveness;

(C) That each active ingredient or animal drug intended for at least one use that is different from all other active ingredients or animal drugs used in the combination provides appropriate concurrent use for the intended target animal population; and

(D) That the active ingredients or animal drugs intended for use in drinking water are physically compatible if FDA, based on scientific information, has reason to believe the active ingredients or animal drugs are physically incompatible.

(3) *Other combination new animal drugs.* For all other combination new animal drugs, the sponsor shall demonstrate by substantial evidence, as defined in this section, that the combination new animal drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling and that each active ingredient or animal drug contributes to the effectiveness of the combination new animal drug.

4. Section 514.111 is amended by revising paragraph (a)(5) to read as follows:

§ 514.111 Refusal to approve an application.

(a) * * *

(5) Evaluated on the basis of information submitted as part of the application and any other information before the Food and Drug Administration with respect to such drug, there is lack of substantial evidence as defined in § 514.4.

* * * * *

Dated: July 21, 1999.

William K. Hubbard,

Senior Associate Commissioner for Policy, Planning and Legislation.

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DEPARTMENT OF TRANSPORTATION

National Highway Traffic Safety Administration

Federal Highway Administration

23 CFR Parts 1200 and 1205

[Docket No. NHTSA–99–6011]

RIN 2127–AH53

Uniform Procedures for State Highway Safety Programs

AGENCY: National Highway Traffic Safety Administration and Federal Highway Administration, DOT.

ACTION: Final rule.

SUMMARY: This final rule announces that amendments to the regulation establishing uniform procedures for