provide other means of verification satisfactory to the Secretaries in these situations.

The proposed rule does not contain policies with Federalism implications sufficient to warrant preparation of a Federalism assessment under Executive Order 12612.

Regulatory Flexibility Act. In accordance with the Regulatory Flexibility Act, 5 U.S.C. 601 *et seq.*, the Assistant General Counsel for Legislation and Regulation has certified to the Chief Counsel, Small Business Administration, that the proposed rule will not have a significant economic impact on a substantial number of small entities. This is because the rulemaking is primarily to make technical changes.

Paperwork Reduction Act. This rulemaking involves information collection activities subject to the Paperwork Reduction Act of 1980, 44 U.S.C. 3501 *et seq.* which is currently approved by the Office of Management and Budget under control number 0625–0134. The amendments would have no effect on the information burden on the public.

Notwithstanding any other provision of the law, no person is required to respond to, nor shall any person be subject to a penalty for failure to comply with a collection of information unless it displays a currently valid OMB Control Number.

It has been determined that the proposed rulemaking is not significant for purposes of Executive Order 12866.

List of Subjects in 15 CFR Part 303

Administrative practice and procedure, American Samoa, Customs duties and inspection, Guam, Imports, Marketing quotas, Northern Mariana Islands, Reporting and recordkeeping requirements, Virgin Islands, Watches and jewelry.

For reasons set forth above, we propose to amend 15 CFR Part 303 as follows:

PART 303—[AMENDED]

§ 303.6 [Amended]

1. Section 303.6(a) is amended by adding to the second to last sentence ‘‘, or verified by other means satisfactory to the Secretaries,’’ after the words U.S. Customs Service.

§ 303.14 [Amended]

2. Section 303.14(e) is amended by removing ‘‘3,100,000’’ and adding ‘‘2,600,000’’ in its place.

Robert S. LaRussa,

Assistant Secretary for Import Administration.

Allen Stayman,

Director, Office of Insular Affairs.

[FR Doc. 97–29198 Filed 11–4–97; 8:45 am]

BILLING CODE 3510–DS–M and 4310–93–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: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA), as directed by the Animal Drug Availability Act of 1996 (ADAA), is proposing to amend its new animal drug regulations to further define the term ‘‘substantial evidence.’’ The purpose of this proposed regulation 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 proposal also encourages dose range labeling.

DATES: Submit written comments on the proposed rule by February 3, 1998. Submit written comments on the information collection requirements by December 5, 1997.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Submit written comments on the information collection requirements to the Office of Management and Budget (OMB), New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, Attn.: Desk Officer for FDA.

FOR FURTHER INFORMATION CONTACT: Herman M. Schoenemann, Center for Veterinary Medicine (HFV–126), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–594–1638.

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 the definition of ‘‘substantial evidence.’’ Section 2(e) of the ADAA directs FDA to issue proposed regulations to further define the term ‘‘substantial evidence’’ in a manner that encourages the submission of NADA's and supplemental NADA's. Section 2(e) also directs FDA to issue proposed regulations to encourage dose range labeling. This proposed regulation further defines substantial evidence and encourages dose range labeling.

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. The demonstration of effectiveness represents a significant component of drug development time and cost such that the amount and nature of the evidence needed can be an important determinant of whether and when new animal drugs become available to the public. The availability of certain approved new animal drugs for use in livestock, poultry, pets, and other animals is vital to protecting the health of animals and the health of humans who consume the products of food producing animals. The availability of other approved new animal drugs is vital to increasing the efficiency of food production in the United States. Thus, animal and human health and food production are best served by the development of substantial evidence of effectiveness in an efficient manner. The changes made to the definition of ‘‘substantial evidence’’ by the ADAA and by the further definition of that term in this proposed 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. The Statutory Definition of Substantial Evidence

The term ‘‘substantial evidence’’ as defined in section 512(d)(3) of the act refers to the number and types of adequate and well-controlled studies needed for a new animal drug to be determined to be effective for the intended uses under the conditions of use prescribed, recommended, or suggested (hereinafter suggested) in its labeling or proposed labeling.

Prior to the enactment of the ADAA, section 512(d)(3) of the act defined substantial evidence as:

[e]vidence consisting of adequate and well-controlled investigations, including field investigation, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, 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 labeling or proposed labeling thereof.

Under section 512(d)(3), as amended by the ADAA, substantial evidence is defined as:

[e]vidence consisting of one or more adequate and well-controlled investigations, such as,

(A) a study in a target species;

(B) a study in laboratory animals;

(C) any field investigation that may be required under this section and that meets the requirements of [section 512 (b)(3) of the act] if a presubmission conference is requested by the applicant;

(D) a bioequivalence study; or

(E) an in vitro study;

by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved 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 labeling or proposed labeling thereof.

Under the old definition, at least two adequate and well-controlled studies were necessary to demonstrate by substantial evidence the effectiveness of a new animal drug and at least one of those adequate and well-controlled studies was required to be a field study. Under the revised definition of substantial evidence it is possible that a minimum of one adequate and well-controlled study [1] may provide substantial evidence of the effectiveness of a new animal drug for its intended uses and associated conditions of use.

Furthermore, the statutory requirement for a field study has been eliminated, but FDA continues to have the authority to require field studies when necessary (H. Rept. 104–823, at 13 (1996)). Elimination of the requirement for a field study recognizes that while a field study (because it assesses the effectiveness of a new animal drug under conditions of use that approximate actual use conditions) remains an important element of many new animal drug approvals, there will be some instances in which a field study would yield no more useful information with regard to the new animal drugs effectiveness than can be obtained through laboratory studies. Thus, the new definition of substantial evidence specifically identifies types of adequate and well-controlled studies that may be used in lieu of, or in addition to, field studies to provide evidence of the effectiveness of a new animal drug.

III. Description of the Proposed Rule

FDA is proposing to amend part 514 (21 CFR part 514) by adding § 514.4 Substantial evidence to further define substantial evidence. Proposed § 514.4 describes the characteristics of substantial evidence that permit qualified experts to fairly and reasonably conclude that the drug will have the effect it purports or is represented to have under the conditions of use suggested in the proposed labeling. The proposed regulation would give FDA flexibility to determine, in light of the current state of relevant scientific knowledge, the minimum number of adequate and well-controlled studies needed, dependent upon the quality and persuasiveness of such studies, to permit qualified experts to conclude that a new animal drug is effective. Substantial evidence must include a sufficient number of studies of sufficient quality to permit experts qualified by scientific training and experience to fairly and reasonably conclude that the new animal drug is effective for each of the intended uses and associated conditions of use suggested in the proposed labeling.

A. Characteristics of Substantial Evidence (§ 514.4(b))

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

Proposed § 514.4(b)(2) requires that the sponsor demonstrate that a new animal drug is effective for each proposed intended use and associated conditions of use. A critical step in deciding the number and types of adequate and well-controlled studies needed to demonstrate effectiveness is to clearly define the intended uses and the associated conditions of use. Intended use refers to the structure or function of the body to be affected or the disease or condition to be treated, prevented, mitigated, or cured. Conditions of use that may be suggested in the proposed labeling for each intended use include, but are not limited to: The dose or dose range, frequency, duration, timing (e.g., in relation to the onset of clinical signs), and route of administration or application of the new animal drug; the withdrawal period (if any); the preparation of the new animal drug for use; the species, age, gender, class, and breed of animal for which the new animal drug is intended for use; and, restriction to use under the supervision of a licensed veterinarian.

The specific number and types of adequate and well-controlled studies needed to provide substantial evidence of effectiveness of a new animal drug will vary depending upon the number of intended uses, how narrowly or broadly each intended use is defined, and, further, upon the conditions of use associated with each intended use suggested in the proposed labeling. Intended uses are the determining factors in selecting the parameters to be measured under the conditions of use proposed for the new animal drug. Because a new animal drug must be shown to be effective for each intended use under the conditions of use suggested in the proposed labeling, the greater the number of intended uses and the more varied the associated conditions of use, the less likely it is that a single study can be designed and conducted to measure all relevant parameters. Likewise, the broader an intended use, e.g., the new animal drug is intended to treat a disease with multiple clinical presentations, the more likely it is that multiple studies will be needed.

One of the most important conditions of use for any new animal drug is the dosage. Dosage includes the dose or dose range, dosing frequency, and the dosing duration. Thus, a sponsor must demonstrate by substantial evidence that a new animal drug is effective for its intended use at the dose or dose range and the associated conditions of use suggested in the proposed labeling for that intended use. The studies needed to make such a demonstration will depend, in part, upon whether the new animal drug is labeled for use at a single fixed dose or over a dose range.

The substantial evidence necessary to support a dose range will further vary with the nature of the new animal drug and its intended uses. Proposed § 514.4(b)(2) provides that 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 at least one intended use at the lower dose limit

[1] The ADAA requires FDA to issue a proposed regulation to further define the term ''adequate and well-controlled'' to require that field investigations be designed and conducted in a scientifically sound manner, taking into account practical conditions in the field and differences between field conditions and laboratory conditions. FDA published a proposed regulation further defining the term ''adequate and well-controlled'' in the **Federal Register** of May 8, 1997 (62 FR 25153).

prescribed in the proposed labeling and will be effective for each intended use at the dose suggested in the proposed labeling for that intended use. The proposed regulation also provides that substantial evidence to support a dose range for a new animal drug intended to affect the structure or function of the body of an animal for the purpose of enhancing production 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 each intended use at all the doses within the range prescribed for the intended use. In either instance, the upper limit of a dose range for any new animal drug will be set based on safety, both to the the target animal and to humans consuming products from animals treated with the new animal drug, as well as practicality, e.g., volume of injection or length of withdrawal period.

The agency notes that a conclusion that a new animal drug is effective for its intended uses no longer requires dose optimization. Prior to enactment of the ADAA in 1996, FDA was required under section 512(d)(1)(F) of the act to refuse to approve a new animal drug if, on the basis of any information before FDA, the tolerance limitation proposed, if any, exceeded that reasonably required to accomplish the physical or other technical effect for which the new animal drug is intended. In order to demonstrate by substantial evidence the minimal amount of a new animal drug reasonably required to accomplish the physical or technical effect, dose optimization, typically supported by adequate and well-controlled dose titration studies that characterize the critical aspects of the dose response relationship, was required. This characterization of the dose-response relationship permitted FDA to make a risk-benefit assessment of the new animal drug. That is, FDA could determine whether the effectiveness of a new animal drug outweighed the risks to the target animal at the dose or over the dose range prescribed in the proposed labeling.

With the enactment of the ADAA, the requirement for dose optimization has been eliminated. It is no longer necessary that the dose or dose range prescribed in the proposed labeling of a new animal drug be limited to that required to accomplish the physical or other technical effect. Therefore, a sponsor is now required to demonstrate by substantial evidence that a new animal drug is effective for each intended use at the associated dose or over the associated dose range prescribed in the proposed labeling. And, the sponsor must demonstrate that such dose or dose range is safe for the target animal and, at the labeled withdrawal time(s), does not result in a residue of such drug in excess of a tolerance found by FDA to be safe.

Although the requirement for dose optimization has been eliminated, sponsors will still need to characterize the critical aspects of the dose response relationship so that qualified experts can make an informed risk-benefit assessment of the new animal drug and assure that the proposed labeling is not false or misleading in any particular. Thus, a sponsor must characterize for an intended use and associated conditions of use the critical aspects of the dose-response relationship relevant to the dose or dose range selected. For example, for new animal drugs intended to affect the structure or function of the body of an animal for the purpose of enhancing production, generally a sponsor should characterize whether the dose or dose range prescribed in the proposed labeling for the new animal drug falls on the part of the dose-response curve at which there is increasing effectiveness or on the part of the dose-response curve at which effectiveness is essentially static, i.e., the plateau. This characterization does not, however, have to be demonstrated by substantial evidence.

FDA encourages the use of dose range labeling. The use of dose range labeling, particularly professional flexible labeling, enhances the ability of users to safely, effectively, and economically treat animals without using the new animal drug in an extra-label manner. As discussed previously, the critical aspects of the dose-response relationship must generally be characterized to support labeling, including dose range labeling. Although many drugs have increasing effectiveness over a definable dose range, most reach a point at which effectiveness is not measurably improved by increased dosing. Without a sufficient characterization of the dose-response relationship, qualified experts cannot determine whether dose range labeling is false or misleading in any particular and the user cannot be adequately informed regarding the appropriate use of the new animal drug.

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

Whether substantial evidence for a particular new animal drug consists of a single adequate and well-controlled study of sufficient quality or one adequate and well-controlled study corroborated by additional adequate and well-controlled studies will depend on the new animal drug involved. Proposed § 514.4(b)(3)(i) provides that studies intended to provide substantial evidence of effectiveness shall consist of a sufficient number of studies of sufficient quality and persuasiveness to permit qualified experts in determining that the parameters reflect the effectiveness of the new animal drug; that the results obtained are likely to be repeatable, and that valid inferences can be drawn to the target animal[2] population; and, that the new animal drug is effective for the intended use at the dose or dose range and associated conditions of use suggested in the proposed labeling.

For each study that is part of substantial evidence, the critical characteristics of identity, strength, quality, purity, and physical form of the new animal drug used must be sufficiently documented to permit meaningful evaluation of the study and comparison with other studies conducted with the new animal drug (proposed § 514.117(b)(3) (62 FR 25153, May 8, 1997)).

For qualified experts to fairly and reasonably conclude that a new animal drug is effective for an intended use under the conditions of use suggested in the proposed labeling for the new animal drug, the study parameters selected for measurement must reliably reflect the effectiveness of the new animal drug for the intended use (selection of study parameters (§ 514.117(b)(3)(i)(A))). A new animal drug cannot be shown to be effective for an intended use without eliciting a measurable response with respect to parameters highly correlated to that intended use of the drug. Generally, a sponsor should evaluate parameters that provide direct evidence of effectiveness with respect to the intended use, but, where appropriate, a sponsor may measure effects on an established surrogate endpoint.

The studies that provide substantial evidence must provide reasonable assurance that the results obtained from the use of the new animal drug are repeatable when the new animal drug is applied or administered under conditions of use suggested in the proposed labeling (repeatability of study results (§ 514.4(b)(3)(i)(B)). The definition of substantial evidence in section 512 of the act prior to its amendment by the ADAA and its requirement for more than one adequate and well-controlled study were based

[2] Target animal and target animal population as used throughout this document refer to the animal or animal population for which the new animal drug is intended for use.

on the principle of independent substantiation. The goal of independent substantiation of experimental results is to ensure that an experimental finding of effectiveness is not the result of: Unanticipated, undetected, or systematic biases; study site-or investigator-specific factors that prevent generalization of the finding to the intended target animal population; or chance. Independent substantiation also provides a safeguard against those rare instances in which the results of a study are the product of fraudulent reporting of scientific studies. Independent substantiation continues to be a primary scientific principle upon which qualified experts can make a determination whether a new animal drug is effective.

Historically, the need for independent substantiation was frequently equated with the need for replication, i.e., replication of an identical study. While replication is usually a highly reliable way to independently substantiate experimental results, it is not the only way. Results obtained from studies that are different in design or execution or both may provide support for a conclusion of effectiveness that is at least as convincing as a repeat of the same study. Under the revised definition of substantial evidence, substantial evidence supporting the effectiveness of a new animal drug for an intended use may be achieved by carefully and properly designing and conducting a single adequate and well-controlled study or by conducting multiple adequate and well-controlled studies that need not replicate one another.

The number of studies needed to provide independent substantiation and support a finding by qualified experts that a new animal drug is effective will depend upon the quality of the studies and the inferential value of the studies. Whatever scientific evidence is needed to demonstrate the effectiveness of a new animal drug, the quality of that scientific evidence is of comparable importance to its quantity. Quality of a study includes factors such as the rigor, power, and scope of the design and conduct of a study, and the sufficiency of the study documentation. As the quality of an effectiveness study improves, the study's reliability, inferential value, and capacity to substantiate effectiveness improves.

Even when intended uses and conditions of use are narrowly defined and there is relevant scientific knowledge to inform qualified experts about the chemical entity, the disease or condition to be treated, or the structure or function to be affected, a single adequate and well-controlled study frequently will not suffice to establish the effectiveness of a new animal drug without the corroboration (independent substantiation) provided by other adequate and well-controlled studies. When considering whether to rely on a single adequate and well-controlled study, it is critical that the possibility of an incorrect outcome be considered and that all available data be examined for their potential to either support or undercut reliance on a single study. In those limited instances in which reliance is placed on a single adequate and well-controlled study that has the characteristics described in § 514.111(a)(5)(ii) (proposed § 514.117 (62 FR 25153, May 8, 1997)), such a study will need to be of sufficient quality, as well as persuasiveness in outcome, to enable qualified experts to make valid inferences from study results to the target animal population. The presence of the following characteristics in a study can contribute to a conclusion by qualified experts that a single adequate and well-controlled study provides substantial evidence of effectiveness: 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; the study involves prospective randomized stratifications or identified analytic subsets that each show a significant effect; the study includes multiple endpoints involving different events; and, the study provides highly reliable and statistically strong evidence of effectiveness. The likelihood that qualified experts can rely on a single adequate and well-controlled study as establishing the effectiveness of a new animal drug increases with the number of these and similar characteristics displayed in the single study.

Inferential value of data (sometimes referred to as generalizability) 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 (§ 514.4(b)(3)(i)(B)) . The inferential value of data may depend upon, among other things, how closely the test animals approximate the characteristics of the target animal population. Time, how recently a particular set of data has been collected, may also affect its inferential value. Animal research data has an effective life span during which time-dependent factors such as genetics of the target animal and the target organism, husbandry practices, and diets remain sufficiently static to assure the continued relevance of the data. Beyond this period, changes in target animal genetics, target organism genetics, husbandry practices, and diets may affect the ability of the new animal drug to achieve the effect demonstrated under prevailing conditions at the time of testing. Time is particularly meaningful in terms of the inferences that can be drawn from data relating to therapeutic uses of antimicrobial animal drugs because of the development of resistant microbes.

Substantial evidence must permit qualified experts to conclude that a new animal drug will have the effect it purports or is represented to have under the conditions of use suggested in the proposed labeling (concluding a new animal drug is effective (§ 514.4(b)(3)(i)(C)). Section 512 of the act requires that FDA issue an order refusing to approve an NADA if there is a lack of substantial evidence that the new animal drug will have the effect it purports or is represented to have under the conditions of use suggested in the proposed labeling. Similarly, the statute requires that FDA issue an order refusing to approve an NADA if, based on a fair evaluation of all the material facts, the proposed labeling is false or misleading in any particular, including as it relates to the demonstrated effectiveness of the new animal drug for its intended uses under associated conditions of use. Thus, sponsors should remember that it may be necessary to provide, in addition to or as part of substantial evidence, evidence that explicit or implicit claims relating to effectiveness made on the label of a new animal drug are neither false nor misleading.

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

Proposed § 514.4(b)(3)(ii) specifies that the types of adequate and well-controlled studies needed to provide substantial evidence may include, but are not limited to, published studies, foreign studies, studies using models, and studies conducted by or on behalf of the sponsor. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered as part of substantial evidence (§ 514.111; proposed § 514.117 (62 FR 25153, May 8, 1997)), and will not contribute to the current state of scientific knowledge that informs qualified experts.

The utility of published studies, foreign studies, and studies using

models as adequate and well-controlled studies to support a finding of effectiveness may vary. The use of published studies raises at least two questions: (1) How reliable are the data? and, (2) do the data represent a skewed subset of information?

Published literature, even in peer-reviewed journals, may not be free from error, omission, misinterpretation, or even outright fraud. Peer reviewers of articles submitted for publication in journals vary in the relevant experience and expertise they may have to review particular journal articles and, typically, only have access to a limited data set and analyses. As noted by Dr. Richard Horton, editor of *The Lancet*, an international biomedical journal, ''* * * the review process will only rarely detect misconduct and it may well miss critical flaws in a research article'' (Ref. 1). Dr. Horton further noted that in instances where legitimate questions are raised about the validity of research methods and data analyses, ''[i]t is possible that the only way to settle the dispute is to provide access to raw data or to invite the institution where the research was conducted to assist in the ongoing investigations'' (Ref. 1). In many instances, published literature is intended to advance science by stimulating further analysis and interpretation. In that sense, some amount of error is not necessarily bad; disputes over analyses and interpretation can drive scientific research and progress (Ref. 1). However, if a sponsor of a new animal drug uses a published study to provide evidence that a new animal drug is effective, use of invalid research methods or invalid data analyses in the study will make the study unacceptable.

FDA's ability to rely on a published study as an adequate and well-controlled study that is part of substantial evidence is enhanced, and in many cases is only possible, if FDA can obtain additional critical study details. The level of scrutiny for such a published study should not be less rigorous than that given to studies conducted by or on behalf of the sponsor that are intended to be adequate and well-controlled studies to support a determination of effectiveness.

Providing as much of the following types of information about a study, in conjunction with the published report, can increase the likelihood that the study can be relied upon as an adequate and well-controlled study: A statement describing the extent, if any, to which the study was funded or supported by the sponsor; the qualifications of the expert who conducted the study; a copy of the protocol, as amended, used for the study, of sufficient detail to permit the study to be reconstructed or repeated; access to written documentation describing the practices followed in the conduct of the study (including identification of animals omitted from analysis, and an analysis of results using all subjects with on-study data); the prospective statistical analysis plan and any changes from the original plan that occurred during or after the study; a full accounting of all investigational animals; an adequate characterization of the new animal drug used in the study; assay data for the new animal drug; and, complete study records including pertinent baseline characteristics for each animal or experimental unit of animals.

In addition to the public debate concerning the reliability of peer-reviewed published data, there has been expressed in recent years concern that published studies represent a skewed subset of all existing information available on a particular subject. While it may not be possible to determine the extent to which the published studies represent a skewed subset of all existing information, the likelihood of reliance on published literature is increased not only by full knowledge about how the studies were conducted but by the availability of a balanced discussion of the published studies listed in the bibliography that both support and raise questions relating to the safety and effectiveness of the new animal drug. The current regulations already require a sponsor to provide as part of its NADA a complete bibliography and a summary of each published study relevant to the intended uses of the new animal drug for which approval is sought (§ 514.1(b)(7)(iv)).

An adequate and well-controlled foreign study may also be relied upon to support a finding by substantial evidence that a new animal drug is effective. The utility of such studies depends upon whether the potential differences such as animal breeds, genetic composition within a breed, diseases, nutrition, and husbandry practices between the foreign country and the United States are sufficiently addressed. There will be instances in which such differences will scientifically limit the applicability of results of foreign studies.

In some instances, model study designs may be appropriate for use in proving the effectiveness of a new animal drug. In order for a model study to be an adequate and well-controlled study that supports a finding that a new animal drug is effective, the model must be validated to establish an adequate relationship of parameters measured and effects observed in the model with one or more significant effects of treatment in the target animal population under actual conditions of use. Proposed § 514.4(b)(3)(ii) requires such validation. If the correlation of parameters measured and effects observed in the model with one or more significant effects of treatment has not been established as part of general scientific knowledge, such correlation must be established scientifically.

The number and types of new studies that need to be conducted by or on behalf of a sponsor to demonstrate by substantial evidence the effectiveness of a new animal drug for a particular intended use will depend upon factors such as: the availability (either publicly or through right of reference) of information about the drug or the active ingredient, and, in some cases, the chemical class to which it belongs, information derived from studies of other approved or unapproved uses of the active ingredient or drug, and information derived from foreign studies if applicable to the proposed use and the target animal population in the United States; whether the nature of the new animal drug or active ingredient, or the proposed claims, makes the new animal drug conducive to in vitro testing or data extrapolation via pharmacokinetic studies; the availability of published studies involving the new animal drug (as discussed previously); and, concern for animal welfare. The science and practice of drug research and development have significantly evolved since the effectiveness requirement for drugs was established in 1962, and this evolution has implications for the number and type of data needed to demonstrate effectiveness of a particular new animal drug. Today, for many disease conditions, there is a greater understanding of pathogenesis, disease stages, treatment modalities and their characteristics, and, frequently, an increased general understanding regarding the activity of a particular chemical entity or related chemical entities in humans or other animals.

Thus, if there is a significant amount of existing relevant scientific knowledge available to inform qualified experts about a chemical entity, such as the effectiveness of a chemical entity in a condition closely related to that for which the new animal drug is intended, about the pathogenesis and stages of the disease or condition to be treated, or the production function (e.g., weight gain or feed efficiency) to be affected, by the chemical entity, fewer new studies may need to be conducted to support FDA's determination of the effectiveness of the

drug for its intended use. Conversely, the less information known about the nature of the chemical entity or about the disease or condition to be treated or the production effect to be achieved, the greater the need for new studies to support a determination of the effectiveness of the new animal drug. If new studies need to be conducted, existing relevant scientific knowledge may, at least, be helpful in designing studies which provide highly reliable and statistically strong evidence of effectiveness.

B. Substantial Evidence for Combination New Animal Drugs (§ 514.4(c))

Under the ADAA, a streamlined approval process was established for certain combination new animal drugs. Section 512(d)(4) of the act provides that, except in the case of a combination new animal drug that is intended for use other than in animal feed or drinking water (hereinafter referred to as ''dosage form combination new animal drugs'')[3] and contains a nontopical antibacterial ingredient or animal drug, FDA will not refuse to approve an application for a dosage form combination new animal drug that contains active ingredients or animal drugs that have previously been separately approved on grounds that there is a lack of evidence of effectiveness if the sponsor: (1) Demonstrates by substantial evidence that each 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 effectiveness, and (2) demonstrates (a) 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 (b) if FDA has a scientific basis to believe the active ingredients or animal drugs may be incompatible or have disparate dosing regimens, that the active ingredients or animal drugs are physically compatible and do not have disparate dosing regimens (section 512(d)(4)(C) of the act). FDA will not refuse to approve an application for a combination new animal drug that is intended for use in animal feed or drinking water and contains active ingredients or animal drugs that have previously been separately approved on grounds that there is a lack of evidence of effectiveness if the sponsor: (1) Demonstrates by substantial evidence that each active ingredient or animal drug intended only for the same use as another active ingredient or animal drug in the combination, and, if there is more than one than one antibacterial ingredient or animal drug, each antibacterial ingredient or animal drug, makes a contribution to labeled effectiveness, and (2) demonstrates (a) that each active ingredient or animal drug that is intended for at least one use that is different from all other active ingredients or animal drugs in the combination provides appropriate concurrent use for the intended target animal population, and (b) if FDA has a scientific basis to believe the active ingredients or animal drugs intended for use in drinking water may be incompatible, that the active ingredients or animal drugs are physically compatible (section 512(d)(4)(D) of the act). For all other combination new animal drugs, FDA will not refuse to approve an application on the grounds that there is a lack of evidence of effectiveness if the sponsor demonstrates by substantial evidence that the combination new animal drug will have the effect it purports or is represented to have under the conditions of use suggested in the proposed labeling for the combination new animal drug and that each active ingredient or animal drug contributes to the effectiveness of the combination new animal drug.

To implement these statutory provisions, proposed § 514.4(c)(1)(i) defines a combination new animal drug as 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. The substantial evidence necessary to support a conclusion by qualified experts that a combination new animal drug is effective will vary depending upon the active ingredients or animal drugs used in the combination.

Proposed § 514.4(c)(2) provides that for combination new animal drugs that contain 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 (hereinafter ''previously been separately approved''), except in the case of a combination new animal drug that is intended for use other than in animal feed or drinking water that contains a nontopical antibacterial ingredient or animal drug, a sponsor must demonstrate by substantial evidence, as defined in section 512(d)(3) of the act and this proposed regulation, 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. For combination new animal drugs that contain active ingredients or animal drugs that have previously been separately approved for use in animal feed or drinking water and contain more than one antibacterial ingredient or animal drug, the sponsor must also demonstrate by substantial evidence, as defined in section 512(d)(3) of the act and this proposed regulation, that each antibacterial makes a contribution to labeled effectiveness.

Proposed § 514.4(c)(3) provides that for all other combination new animal drugs (i.e., those that contain active ingredients or animal drugs that have not previously been separately approved and those that are dosage form combination new animal drugs that contain an active ingredient or animal drug that is a nontopical antibacterial), the sponsor must demonstrate by substantial evidence, as defined in section 512(d)(3) of the act and this proposed regulation, that: (1) The combination new animal drug will have the effect it purports or is represented to have under the conditions of use suggested in the proposed labeling, and (2) each active ingredient or animal drug contributes to the effectiveness of the combination new animal drug.

On occasion, FDA may have a substantiated scientific basis for believing that the use in combination of active ingredients or animal drugs that have previously been separately approved will result in a decrease in the effectiveness of one or more of the active ingredients or animal drugs. Although section 512(d)(4) of the act generally provides for a modified approval process for combination new animal drugs containing active ingredients or animal drugs that have previously been separately approved, FDA will, to the extent necessary, require additional testing to characterize the effectiveness of such a combination new animal drug to assure that the labeling will not be false or misleading in any particular, consistent with section 512(d)(1)(H) of the act.

For purposes of determining the substantial evidence necessary to demonstrate the effectiveness of a combination of animal drugs that have

[3] Use of the phrase ''dosage form combination new animal drugs'' as used in this preamble is a shorthand reference to combination new animal drugs ''intended for use other than in animal feed or drinking water,'' the purpose of which is to make the complex preamble discussion relating to combination new animal drugs more readable. The term ''dosage form,'' outside of the discussion in this preamble relating to the combination new animal drug provisions of the act, includes and will continue to include new animal drugs intended for use in drinking water.

previously been separately approved, each animal drug brings with it to the combination each intended use for which it was previously separately approved under the conditions of use proposed for the combination new animal drug. If an active ingredient or animal drug has previously been separately approved as a prescription animal drug or a veterinary feed directive drug for any of the intended uses and conditions of use suggested in the proposed labeling for the combination new animal drug, the combination new animal drug, if approved, would usually need to be approved as a prescription animal drug or veterinary feed directive drug, respectively.

1. Antibacterial Active Ingredient or Animal Drug

The approval process provided by section 512(d)(4) of the act does not apply to dosage form combination new animal drugs if any of the active ingredients or animal drugs is a nontopical antibacterial. And, for combination new animal drugs intended for use in animal feed and drinking water that contain more than one antibacterial and qualify for approval under the process provided by section 512(d)(4), a sponsor must demonstrate by substantial evidence that each antibacterial ingredient or animal drug contributes to the effectiveness of the combination new animal drug. The act, as amended by the ADAA, treats antibacterial ingredients and animal drugs differently from other active ingredients and animal drugs because increasingly there are concerns that overuse or improper use of antibacterials may contribute unnecessarily to the development of antibacterial resistance.

Proposed § 514.4(c)(1)(ii) defines an ''antibacterial'' with respect to a particular target animal species as an active ingredient or animal drug: (1) That is approved for use in that species for the diagnosis, cure, mitigation, treatment, or prevention of bacterial disease; or (2) that is approved in that species for any other use that is attributable to its antibacterial properties.

2. Appropriate Concurrent Use and Compatibility

Section 512(d)(4)(C) and (d)(4)(D) of the act requires that in certain cases appropriate concurrent use and compatibility must be demonstrated. The demonstration need not be by substantial evidence but sponsors must provide a scientifically sound basis for qualified experts to reach these conclusions. Proposed § 514.4(c)(2)(iii) sets out the requirement for sponsors to establish appropriate concurrent use for the target species in cases in which each active ingredient or animal drug is intended for at least one use that is different from all the other active ingredients or animal drugs in the combination. To determine whether a combination new animal drug provides ''appropriate concurrent use'' the agency will consider factors such as whether the conditions to be treated by the combination are likely to occur simultaneously with sufficient frequency in the intended target animal population.

Proposed § 514.4(c)(2)(iv) and (c)(2)(v) sets out the requirements in section 512(d)(4)(C)(iii) and (d)(4)(D)(iv) of the act regarding compatibility. These requirements apply where, based on scientific information, FDA has reason to believe that for dosage form combination new animal drugs the active ingredients or animal drugs may be physically incompatible or have disparate dosing regimens or that for active ingredients or animal drugs intended for use in drinking water the active ingredients or animal drugs may be physically incompatible. The legislative history of ADAA describes the purpose of these provisions as ''authoriz[ing] FDA to deny approval of a combination animal drug if the physical compatibility or compatibility of the dosing regimens may affect the effectiveness of the combination animal drug and such compatibility is not demonstrated'' (H. Rept. 104–823 at 14 (1996)).

Scientific information exists that gives FDA reason to believe that dosage form combinations and combinations intended for use in drinking water may be physically incompatible and/or have disparate dosing regimens. With the enactment of the Generic Animal Drug Patent Term Restoration Act of 1988 (GADPTRA), it was well-recognized that, based on scientific information, the bioavailability of active ingredients may be affected by changes relating to the formulation or manufacture of a generic new animal drug and, therefore, the statute, rather than assuming bioequivalence based on the use of the same active ingredient, requires a demonstration of bioequivalence. Similarly, the bioavailability of an active ingredient or animal drug as part of a combination new animal drug may be affected by changes relating to the formulation or manufacture of the active ingredient or animal drug for use in the combination or to the formulation and manufacture of the combination new animal drug. Thus, FDA has scientific information that gives it reason to generally believe that active ingredients or animal drugs intended for use in a dosage form combination new animal drug may not be physically compatible and may have disparate dosing regimens or that for active ingredients or animal drugs intended for use in drinking water the active ingredients or animal drugs may not be physically compatible. Therefore, proposed § 514.4(c)(2)(iv) and (c)(2)(v) requires the sponsor to demonstrate the comparable bioavailability of the active ingredients or animal drugs in combination relative to the active ingredients or animal drugs singly. However, as with FDA's implementation of GADPTRA, certain classes of products are recognized to be of less concern with respect to potential differences in bioavailability, e.g., true solutions, inhalant anesthetics and some topicals. In such cases, some or all of the demonstration of comparable in vivo bioavailability may be waived. The proposed rule provides for such waivers where appropriate.

C. Conclusion

The basic premise underlying the modified requirement for demonstrating the effectiveness of particular combination new animal drugs is that there exists knowledge about the individual active ingredients or animal drugs contained in that combination. This knowledge exists in the approved applications in the form of substantial evidence of effectiveness of the individual active ingredients or animal drugs. The substantial evidence supporting the effectiveness of an approved active ingredient or animal drug generally is not publicly available but is usually owned by the sponsor of the approved application for the active ingredient or animal drug. Thus, the sponsor submitting an application for a combination new animal drug must either own the underlying applications or obtain a right of reference from the owners of such applications if FDA is to rely upon the substantial evidence contained in those applications.

Sponsors may submit supplemental NADA's and receive supplemental approval of new animal drugs for new intended uses. The approval of a new intended use for a single active ingredient new animal drug that has already been approved for use in a combination new animal drug may necessitate the submission of a new or supplemental application for the combination new animal drug. Such new or supplemental NADA for the combination new animal drug must contain substantial evidence of effectiveness in accordance with this

proposed regulation. Sponsors cannot circumvent approval requirements relating to the effectiveness of a combination new animal drug by adding or deleting intended uses to or from any of the new animal drugs approved for use in the combination subsequent to the approval of the combination new animal drug. Section 512(e)(1)(F) of the act would require withdrawal of an existing approval for the combination new animal drug unless the sponsor submits and FDA approves a supplement to the combination NADA that provides adequate information supporting any changes affecting its safety or effectiveness beyond the variations provided for in the approved application.

FDA recognizes that the requirements for obtaining approval of combination new animal drugs are complex. Following the Good Guidance Practices established in the **Federal Register** of February 27, 1997 (62 FR 869691), FDA's Center for Veterinary Medicine (CVM) intends to develop, for public comment, one or more draft guidance documents representing the agency's current thinking on what information should be included in NADA's to support combination new animal drugs.

In all instances, FDA encourages sponsors to meet with CVM to discuss the development of evidence of safety and effectiveness to support approval of an NADA for single ingredient or combination new animal drugs. In considering the number and types of the adequate and well-controlled studies needed to demonstrate the effectiveness of a new animal drug, the sponsor may also want to discuss with FDA any possible later expansion or extension of the claims for the new animal drug so that the studies conducted in support of the initially proposed intended uses will, to the extent possible, facilitate later approvals.

FDA has chosen to define substantial evidence, consistent with the spirit of the ADAA, in a manner that permits the maximum flexibility in determining what studies are necessary to demonstrate by substantial evidence that a new animal drug is effective. While specificity brings with it consistency and predictability, the spirit of the ADAA is flexibility, efficiency, and greater animal drug availability. FDA believes that consistency and predictability can be maintained by the application of sound science.

IV. Conforming Changes

This proposed rule would make necessary conforming changes to §§ 514.1(b)(8) and 514.111 of the current regulations.

V. Environmental Impact

FDA has carefully considered the potential environmental impacts of this proposed rule. The agency has 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.

VI. Analysis of Economic Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and under 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). FDA believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order. The proposed rule is not a significant regulatory action as defined by the Executive Order.

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 proposed labeling. The purpose of the proposed rule further defining substantial evidence is to encourage the submission of NADA's, the submission of supplemental NADA's, and the use of dose range labeling. Accordingly, the proposed 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 FDA would find demonstrate the effectiveness of any particular new animal drug. For example, under the new statutory 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 proposed rule is not expected to impose any new marginal 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 is expected to be a small benefit to sponsors.

Further, the revised definition allows for the submission of as few as one adequate and well-controlled study, whereas the previous statutory language required at least two studies. While FDA expects that the instances in which a single study will be sufficient to demonstrate effectiveness will be limited, those sponsors who are able to demonstrate effectiveness by a single adequate and well-controlled study are likely to realize lower drug development costs.

The proposed rule also provides for 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 is no longer required, sponsors are no longer required to conduct adequate and well-controlled in vivo dose titration studies, but need only conduct such studies as may be needed to characterize the dose or dose range so that FDA can make a risk-benefit assessment and assure 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 characterize the dose-response relationship, sponsors are expected to realize a small cost savings.

Finally, the proposed 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. This change is expected to provide a cost savings to the sponsors of NADA's that meet the criteria for the streamlined approval process.

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 economic impact

on a substantial number of small entities. As this proposed regulation 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 proposed 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.

VII. 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 annual expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation). This proposed rule does not impose any mandates on State, local, or tribal governments, or the private sector that will result in an annual expenditure of $100,000,000 or more.

VIII. Paperwork Reduction Act of 1995

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

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

Title: Substantial Evidence of Effectiveness of New Animal Drugs.

Description: As directed by the ADAA, FDA is publishing a proposed regulation 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 proposed 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 proposed regulation, § 514.4(a), 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. The proposed regulation will reduce the number of adequate and well-controlled studies necessary to demonstrate the effectiveness of certain combination new animal drugs, will eliminate the need for an adequate and well-controlled dose titration study, and may, in limited instances, reduce or eliminate the number of adequate and well-controlled field investigations necessary to demonstrate by substantial evidence the effectiveness of a new animal drug.

Table 1 below represents the estimated burden of meeting the new substantial evidence standard. The numbers in the chart are based on recent consultation with several of the major research and development firms that conduct the majority of studies submitted to establish substantial evidence of effectiveness of new animal drugs. Because of the more flexible requirements for demonstrating substantial evidence of effectiveness, FDA estimates 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.

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN

21 CFR	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

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

In compliance with section 3507(d) of the PRA of 1995, the agency has submitted the information collection provisions of this proposed rule to OMB for review. Interested persons are requested to send comments regarding information collection by December 5, 1997 to the Office of Information and Regulatory Affairs, Office of Management and Budget, New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, Attn.: Desk Officer for FDA.

IX. References

The following information has been placed on display in the Dockets Management Branch and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Horton, Richard, ''Revising the Research Record,'' *The Lancet*, vol. 346, p. 1610–11, 1995.

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.* Studies that are intended to provide 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.* Studies that are intended to provide substantial evidence of the 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. 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 at least one intended use at the lower dose limit prescribed in the proposed labeling and will be effective for each intended use at the dose suggested in the proposed labeling for that intended use. Substantial evidence to support a dose range for a new animal drug intended to affect the structure or function of the body of an animal for the purpose of enhancing production 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 each intended use at all the doses within the range prescribed for the intended use. 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.

(3) *Studies*—(i) *Number.* Substantial evidence of the effectiveness of a new animal drug for an 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*—(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) For purposes of this section, antibacterial with respect to a particular target animal species means an active ingredient or animal drug:

(A) That is approved in that species for the diagnosis, cure, mitigation, treatment, or prevention of bacterial disease; or

(B) That is approved for use in that species for any other use that is attributable to its antibacterial properties.

(2) *Combinations with active ingredients or animal drugs that have previously been separately approved.* Except in the case of a combination new animal drug intended for use other than in animal feed or drinking water that contains a nontopical antibacterial ingredient or animal drug, for combination new animal drugs that contain 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 incorporate into the application for the combination new animal drug substantial evidence of the effectiveness of each active ingredient or animal drug previously approved and shall demonstrate:

(i) 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;

(ii) For such combination new animal drugs that are intended for use in animal feed or drinking water and 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;

(iii) 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;

(iv) Unless waived in specific cases, that the active ingredients or animal drugs intended for use other than in animal feed or drinking water are physically compatible and do not have disparate dosing regimens by demonstrating bioavailability of the active ingredients or animal drugs in combination relative to the bioavailability of active ingredients or animal drugs singly; and,

(v) Unless waived in specific cases, that the active ingredients or animal drugs intended for use in drinking water are physically compatible by demonstrating bioavailability of the active ingredients or animal drugs in combination relative to the bioavailability of active ingredients or animal drugs singly;

(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: October 30, 1997.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 97–29275 Filed 10–31–97; 2:48 pm]

BILLING CODE 4160–01–F

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 58

[AD–FRL–5903–6]

RIN 2060–AF71

Ambient Air Quality Surveillance for Lead

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: Lead air pollution levels measured near the Nation's roadways have decreased 97 percent between 1976 and 1995 with the elimination of lead in gasoline used by on-road mobile sources. Because of this historic decrease, EPA is shifting its ambient air monitoring focus from measuring lead air pollutant concentrations emanating from mobile source emissions toward a focus on stationary point sources of lead air pollution. Today's action proposes to revise the part 58 lead air monitoring regulations to allow many lead monitoring stations to be discontinued while maintaining a core lead monitoring network in urban areas to track continued compliance with the lead National Ambient Air Quality Standards (NAAQS). This action also requires lead ambient air monitoring around lead stationary sources. This action is being taken at the direct request of numerous State and local agencies whose on-road mobile source-oriented lead monitors have been reporting peak lead air pollution values that are many times less than the quarterly lead NAAQS of 1.5μg/m³ for many years. Approximately 70 of the National Air Monitoring Stations (NAMS) and a number of the State and Local Air Monitoring Stations (SLAMS) could be discontinued with this action, thus making more resources available to those State and local agencies to deploy lead air quality monitors around heretofore unmonitored lead stationary sources.

DATES: Comments must be submitted on or before December 5, 1997.

ADDRESSES: Comments should be submitted (in duplicate, if possible) to: Air Docket (LE–131), US Environmental Protection Agency, Attn. Docket No. A–91–22, 401 M Street, SW, Washington, D.C. 20460.

FOR FURTHER INFORMATION CONTACT: Brenda Millar, Emissions, Monitoring, and Analysis Division (MD–14), Office of Air Quality Planning and Standards, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711, Telephone: (919) 541–4036, e-mail:millar.brenda@email.epa.gov.

SUPPLEMENTARY INFORMATION:

I. Authority

Sections 110, 301(a), and 319 of the Clean Air Act as amended 42 U.S.C. 7410, 7601(a), 7619.

II. Background

The current ambient air monitoring regulations that pertain to lead air sampling were written in the 1970's when lead emissions from on-road mobile sources (e.g., automobiles, trucks) were the predominant lead air emission source affecting our communities. As such, the current lead monitoring requirements focus primarily upon the idea of determining the air quality impacts from major roadways and urban traffic arterial highways. Since the 1970's, lead has been removed from gasoline sources for on-road vehicles (on-oad vehicles now account for less than 1 percent of total lead emissions), and a 97 percent decrease in lead air pollution levels measured in our neighborhoods and near roadways has occurred nationwide. Because of this historic decrease, EPA is reducing its requirements for measuring lead air pollutant concentrations near major highways, and is focusing on stationary point sources and their impacts on neighboring populations.

The current lead air monitoring regulations require that each urbanized area with a population of 500,000 or more operate at least two lead NAMS, one of which must be a roadway-oriented site and the second must be a neighborhood site with nearby traffic arteries or other major roadways. There are approximately 85 NAMS in operation and reporting data for 1996. This action would reduce this NAMS requirement to include one NAMS site in one of the two largest Metropolitan Statistical Areas (MSA/CMSA) within each of the ten EPA Regions, and one NAMS population-oriented site in each populated area (either a MSA/CMSA, town, or county) where lead violations have been measured over the most recent 8 calendar quarters. This latter requirement is designed to provide information to citizens living in areas that have one or more lead stationary sources that are causing recent air quality violations. At present, the MSA/CMSAs, cities, or counties that have one or more quarterly Pb NAAQS violations that would be subject to this requirement include:

TABLE 1.—CMSA/MSA'S OR COUNTIES WITH ONE OR MORE LEAD NAAQS VIOLATIONS IN 1995–1996

CMSA/MSA or county	Contributing lead source(s)
Philadelphia-Wilmington-Atlantic City CMSA	Franklin Smelter in Philadelphia County, PA.
Tampa-St. Petersburg-Clearwater MSA	Gulf Coast Lead in Hillsborough County, FL.
Memphis MSA	Refined Metals in Shelby County, TN.
Nashville MSA	General Smelting in Williamson County, TN.
St. Louis MSA	Chemetco in Madison County, IL, and Doe Run in Jefferson County, MO.
Cleveland-Akron CMSA	Master Metals in Cuyahoga County, OH.
Iron County, MO	ASARCO in/near Hogan, MO.