Greenwood, MS, Greenwood-Leflore, NDB or GPS RWY 18, Amdt 1A
Minden, NE, Pioneer Village Field, VOR or GPS RWY 34, Amdt 1A CANCELLED
Minden, NE, Pioneer Village Field, VOR RWY 34, Amdt 1A
Ocean City, NJ, Ocean City Muni, VOR or GPS RWY 6, Amdt 1 CANCELLED
Ocean City, NJ, Ocean City Muni, VOR RWY 6, Amdt 1
Teterboro, NJ, Teterboro, VOR/DME RNAV or GPS RWY 24, Orig-B CANCELLED
Teterboro, NJ, Teterboro, VOR/DME RNAV RWY 24, Orig-B
Shirley, NY, Brookhaven, VOR or GPS RWY 6, Amdt 2 CANCELLED
Shirley, NY, Brookhaven, VOR RWY 6, Amdt 2
Clemson, SC, Clemson-Oconee County, VOR/DME or GPS RWY 25, Orig-A CANCELLED
Clemson, SC, Clemson-Oconee County, VOR/DME RWY 25, Orig-A
Cedar City, UT, Cedar City Muni, NDB or GPS RWY 20, Orig CANCELLED
Cedar City, UT, Cedar City Muni, NDB RWY 20, Orig
Fredericksburg, VA, Shannon, VOR or GPS RWY 24, Amdt 7 CANCELLED
Fredericksburg, VA, Shannon, VOR RWY 24, Amdt 7
Spokane, WA, Spokane Intl, VOR or GPS RWY 3, Amdt 12 CANCELLED
Spokane, WA, Spokane Intl, VOR RWY 3, Amdt 12
Ravenswood, WV, Jackson County, VOR/DME or GPS RWY 3, Amdt 2A CANCELLED
Ravenswood, WV, Jackson County, VOR/DME RWY 4, Amdt 2A

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 514

[Docket No. 97N–0141]

Adequate and Well-Controlled Studies for Investigational Use and Approval 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 regulations governing new animal drug applications to further define the term ''adequate and well-controlled studies.'' The purpose of this final rule is to further define ''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.

DATES: The regulations are effective on April 6, 1998.

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. Section 2(e) of the ADAA directs FDA to issue, within 18 months of its enactment, final regulations 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. In an advance notice of proposed rulemaking that published in the **Federal Register** of November 21, 1996 (61 FR 59209), FDA solicited comments from interested parties on how to further define ''adequate and well controlled as it relates to field studies.'' [1] Docket No. 96N–0411 was created for comments responding to this notice.

In the **Federal Register** of May 8, 1997 (62 FR 25153), FDA proposed to amend its regulations in part 514 (21 CFR part 514) to further define the term ''adequate and well-controlled studies.'' FDA provided 75 days for public comment on the proposed rule. Docket No. 97N–0141 was created for comments regarding this proposed rule. As proposed, one of the characteristics of an adequate and well-controlled study is that such a study, when conducted in target animals, be conducted in compliance with ''good study practices'' (GSP's). Elsewhere in the **Federal Register** of May 8, 1997 (62 FR 25152), FDA reopened Docket No. 96N–0411 and gave interested parties 30 days to comment on GSP's.

The primary purpose of conducting adequate and well-controlled studies is, and has always been, to distinguish the effect of the drug from other influences, such as spontaneous change in the course of disease and biased observation, so that it can be determined whether the drug is effective. This final rule defines the essential characteristics of adequate and well-controlled studies and explicitly addresses differences between field and laboratory studies.

[1] The terms field investigation and field study are used interchangeably in this final rule.

II. Comments on the Proposed Rule

FDA received two letters, one from the Animal Health Institute (AHI) and one from the Coalition for Animal Health (the Coalition), commenting on the proposed definition of ''adequate and well-controlled studies.'' FDA also received three letters in response to its reopening Docket No. 96N–0411 for comments specifically on GSP's. Comments relating to GSP's can be found in that docket. FDA met with representatives of the Coalition on June 11, 1997, and July 11, 1997, to discuss the proposed rule and GSP's. Those discussions were recorded in memoranda of meeting that have been placed in the docket for the proposed rule, Docket No. 97N–0141, and in Docket No. 96N–0411.

In general, the comments agreed that the characteristics of an adequate and well-controlled study set forth in the proposed regulation represent sound scientific principles essential for adequate and well-controlled studies. However, the comments criticized FDA's failure to address more explicitly in the proposed regulation the differences between field and laboratory studies and objected to FDA's reference to GSP's.

A. Section 514.117(a)

1. AHI recommended that FDA clarify in proposed § 514.117(a) that reports of adequate and well-controlled studies refer to reports of adequate and well-controlled ''effectiveness'' studies. Based on the following discussion, FDA does not find it necessary to make such a clarification.

Under section 512(d)(1)(E) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360b(d)(1)(E)), FDA must refuse to approve a new animal drug application if there is a lack of substantial evidence that the drug will have the effect it is purported or represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling. By definition, substantial evidence consists of one or more adequate and well-controlled studies on the basis of which experts qualified by scientific training and experience to evaluate the effectiveness of the drug could fairly and reasonably conclude that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling (section 512(d)(3) of the act). Thus, it is clear and well established that adequate and well-

controlled studies are studies intended to determine whether or not a drug is effective.

Because it is adequate and well-controlled studies and not just reports of adequate and well-controlled studies that provide a basis for determining whether a new animal drug is effective, and in some instances support a claim of target animal safety, FDA is deleting ''Reports of'' in the second to last sentence in proposed § 514.117(a).

In that same sentence, FDA is also clarifying that adequate and well-controlled studies may be relied upon to support target animal safety but are not necessary to support claims of target animal safety. Studies intended to demonstrate safety need not be adequate and well-controlled studies (see section 512(d)(1) of the act, which states that in order to secure approval of a new animal drug, a sponsor must conduct adequate tests by all methods reasonably applicable to show whether or not such drug is safe). In proposed § 514.117(a), FDA intended only to note that adequate and well-controlled studies intended to demonstrate whether a new animal drug is effective may be designed in a manner that also permits sponsors to simultaneously collect target animal safety data. If a sponsor needs to demonstrate through a field study that a new animal drug is safe for use in the target animal, the sponsor may do so by adequate tests by methods that are reasonably applicable or as part of an adequate and well-controlled study that is designed to determine the effectiveness of the new animal drug. Accordingly the second to last sentence in § 514.117(a) will now provide that adequate and well-controlled studies, in addition to providing a basis for determining whether a new animal drug is effective, may also be relied upon to support target animal safety.

B. Section 514.117(b)(2)

Proposed § 514.117(b)(2) would require that adequate and well-controlled studies conducted in target animals be conducted in compliance with GSP's. In comments to Docket Nos. 96N–0411 and 97N–0141, both the Coalition and AHI strongly opposed the inclusion by reference of GSP's and proposed that a specific provision addressing the differences between field and laboratory studies be added.

1. Objections to GSP's

2. Although the Coalition is not opposed in concept to the development of a standard of conduct of studies in target animals, the Coalition believes that reference to ''good study practices'' should be removed from the further definition of adequate and well controlled and questions whether the standard of conduct must be codified into regulations or whether a guidance may be sufficient. In a submission to Docket No. 96N–0411 stating its objections to the inclusion of GSP's in the definition of adequate and well-controlled studies, AHI cited four concerns as follows: (1) GSP regulations are outside of the scope of the legislation; (2) establishing GSP's will improperly interfere with prompt implementation of the ADAA; (3) discussion of GSP's should be deferred until FDA and industry have adequate experience in using Guidance Document 58, ''Guidance for Industry for Good Target Animal Study Practices: Clinical Investigators and Monitors,'' issued by FDA's Center for Veterinary Medicine (CVM) in May 1997; and (4) GSP's could have a serious negative impact on current and future international harmonization efforts.

AHI and the Coalition consider GSP's to be outside the scope of the ADAA because there is no requirement in the ADAA for GSP's, and because GSP's would apply to any study in the target animal. A study in the target animal may be conducted to evaluate the safety or the effectiveness of a new animal drug. The purpose of the ADAA was to responsibly streamline effectiveness requirements. It was not the intention of the ADAA to modify the standard for determining whether a new animal drug is safe. Thus, it is perceived by AHI and the Coalition that FDA acted outside the directives of the ADAA.

FDA believed that it was in fact being responsive to the directives of the ADAA when it proposed GSP's as a new characteristic of adequate and well-controlled studies. As FDA explained in the preamble to the proposed regulation, the characteristics of an adequate and well-controlled study listed in current § 514.111(a)(5)(ii) remain sound scientific principles essential for all adequate and well-controlled studies. These principles, including use of an appropriate control and procedures to minimize bias, relate primarily to the design of an adequate and well-controlled study. At the same time, FDA acknowledged that the practices that apply to the testing of new animal drugs under field conditions may need to differ from the practices applied to the testing of new animal drugs under laboratory conditions. Good study practices was intended to be the standard of conduct specifically designed for field studies.

The primary purpose of any adequate and well-controlled study is to distinguish, by comparison with appropriate controls, the effect of the new animal drug from other influences so that it can be determined whether or not the new animal drug is effective. A further purpose of an adequate and well-controlled field study is to observe the new animal drug's effects under conditions which closely approximate the conditions under which the new animal drug will be applied or administered. Thus, as discussed in the legislative history of the ADAA (H. Rept. 104–823, at 13 (1996)) and as FDA has repeatedly stated in discussions with the Coalition (see, e.g., Memorandum of July 11, 1997, meeting with the Coalition for Animal Health, Docket No. 97N–0141), it is not expected that sponsors need to or should control all environmental factors, husbandry practices, and other such factors in studies conducted under field conditions. Adequate and well-controlled field studies should balance the need to control the environment and other factors with the need to observe the drug's effects under closely approximated use conditions so that the true effect of the animal drug can be measured and an appropriate inference can be drawn regarding the effect of the animal drug in actual use. Nonetheless, it is critical that the study documentation completely and accurately reflect the conditions under which the new animal drug was tested so that the sponsor and FDA can properly evaluate the study results.

The purpose of requiring compliance with GSP's as a characteristic of an adequate and well-controlled study in the proposed rule was to make it clear that it was not FDA's expectation that the standard of conduct for laboratory studies applied to the conduct of studies under field conditions. By virtue of its inclusion in the definition of adequate and well controlled, the applicability of the standard was limited to any study in the target animal intended to demonstrate the effectiveness of the new animal drug. FDA did not provide further definition of GSP's as part of the definition of adequate and well controlled because FDA believes, as the Coalition notes in its July 22, 1997, comments to Docket No. 97N–0141, that GSP's represent a significant new regulatory concept that requires serious consideration and discussion. Thus, FDA reopened Docket No. 96N–0411 to receive comments from interested parties.

In response to comments opposing the inclusion of GSP's in the definition of adequate and well-controlled studies, FDA is removing the reference in § 514.117(b)(2) to GSP's and replacing it

with a reference to ''an appropriate standard.'' By referencing an appropriate standard, § 514.117(b)(2) allows the application of Good Laboratory Practices (GLP's) to adequate and well-controlled laboratory studies and the application of an as yet to be defined standard of conduct to adequate and well-controlled field studies. Until a guidance or regulations defining the appropriate standard of conduct for conducting adequate and well-controlled studies under field conditions are finalized, FDA will, on its own initiative, waive the requirement for compliance with an appropriate standard of conduct for field studies (§ 514.117(d)) and the study report for an adequate and well-controlled study need not contain a statement describing adherence to an appropriate standard. In the meantime, sponsors can continue to refer to FDA's guidance, ''Good Target Animal Study Practices: Clinical Investigators and Monitors,'' for guidance regarding the responsibilities of investigators and monitors who conduct clinical studies.

Issues to be resolved regarding the development of an appropriate standard of conduct include: (1) What the standard of conduct for field studies should be, (2) whether the standard of conduct should be defined in guidance or by regulation, and (3) whether the standard of conduct should be applied to field studies intended to demonstrate the safety of the new animal drug as well as to adequate and well-controlled field studies intended to demonstrate the effectiveness of the new animal drug.

Although the definition of adequate and well-controlled studies only applies to studies intended to demonstrate the effectiveness of a new animal drug, FDA believes that it is logical that there should be one standard for the conduct of all field studies. The agency believes this to be true because it is the fact that a field study is conducted under field conditions--and not whether the field study is intended to demonstrate safety or effectiveness—that gives rise to the need for a different standard.

In a *Federal Register* notice dated May 8, 1997, that reopened the comment period for Docket No. 96N–0411 and in meetings with the Coalition, FDA asked interested parties to provide FDA with specific examples of how field studies and laboratory studies differ so that FDA can develop a reasonable and appropriate standard of conduct for field studies. No such examples have been provided by any interested parties. FDA intends to continue its efforts to obtain relevant information from interested parties.

As FDA considers further the development of a standard of conduct for field studies, FDA will evaluate its experience in implementing the guidance ''Good Target Animal Study Practices: Clinical Investigators and Monitors.'' However, FDA contemplates that the standard of conduct for field studies will also address issues such as facilities and equipment in addition to those issues addressed in the guidance. Because FDA recognizes the importance of efforts to achieve international harmonization, FDA will also take into consideration the work of the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH), the body responsible for the harmonization of technical requirements for the registration of veterinary medicinal products, relating to the development of standards of conduct for field studies.

2. Explicit Provision to Address Differences Between Field and Laboratory Studies

3. AHI and the Coalition maintain that the further definition of adequate and well controlled should more explicitly take into account practical conditions in the field and the differences between field and laboratory conditions. In its July 22, 1997, comment to Docket No. 97N–0141, the Coalition, on behalf of its member national trade associations including AHI, proposed for inclusion in § 514.117 a paragraph to address the differences between adequate and well-controlled field and laboratory studies. The proposed paragraph read:

Field Investigation. It is recognized that under field conditions, there may be less opportunity for blinding or other traditional non-field controls, such as concurrent placebo or untreated groups. The nature of field trials may preclude the use of a concurrent control group; thus the animal may serve as its own control in selected situations. While the general principles in subparagraph (1) are applicable to a field investigation, conditions on farms, ranches, other animal husbandry operations, and veterinary private practices are such that the same degree of precision with regard to environmental management and documentation of all variables cannot be maintained, as when the trials are conducted on sponsor-owned premises. Controls and documentation must be sufficient to evaluate the investigation, permit the application of statistical methods of evaluation and permit the documentation to be audited.

In response to comments requesting the inclusion of a more explicit provision to address the differences between field and laboratory studies, FDA is revising § 514.117 by redesignating paragraphs (c) and (d) as paragraphs (d) and (e), respectively, and is adding a new paragraph (c). As revised, § 514.117(c) more explicitly addresses the differences between field and laboratory studies.

Unlike the Coalition's suggested language, FDA's provision describing field studies does not discuss at length the use of controls in field studies but instead requires the use of an appropriate control. As discussed in the preamble to the proposed rule (62 FR 25153 at 25154), the sponsor's choice of the type of control used in a study should be based on the scientific, ethical, and practical circumstances associated with that particular study. Section 514.117(b)(6) already states that when the effect of variables such as age, sex, class of animal, severity of disease, duration of disease, dietary regimen, level of animal production, and use of drugs or other therapy is accounted for by an appropriate design, and when, within the same animal, effects due to the test drug can be obtained free of the effects of such variables, the same animal may be used for both the test drug and the control. Consistent with the discussion in the preamble to the proposed rule (62 FR 25153 at 25155) and the American Veterinary Medical Association's comments submitted to Docket No. 96N–0411, FDA's provision reflects the need for field studies to balance the need to control the environment and other factors with the need to observe the drug's performance under actual conditions of use.

C. Section 514.117(b)(3)

4. AHI questioned why the requirements of current § 514.111(a)(3) were changed and greatly expanded by proposed § 514.117(b)(3).

Current § 514.111(a)(3) lists one of the grounds on which FDA may refuse to approve a new animal drug application. Specifically, FDA may refuse to approve a new animal drug application if the methods used in and the facilities and controls used for the manufacture, processing, and packaging of such drug are inadequate to preserve its identity, strength, quality, and purity. Proposed § 514.117(b)(3) does not expand upon the requirements of this section.

Proposed § 514.117(b)(3) describes a characteristic of an adequate and well-controlled study and was intended to correspond to current § 514.111(a)(5)(ii)(b) which provides that the test drug must be standardized in order for a study to be considered adequate. FDA did not provide an explanation of this section because it believed the provision to be clear on its face. The identity, strength, quality, and purity of a new animal drug being tested

in a particular study must be known and be reproducible. Knowledge of this information permits meaningful evaluation of the effectiveness of the new animal drug and allows the appropriate comparison of effectiveness studies in which different formulations of the new animal drug are used. Furthermore, the sponsor of the new animal drug must be able to demonstrate the equivalency of the formulation of the new animal drug proposed for marketing to the formulations used in the study or studies supporting effectiveness and safety. Therefore, FDA has finalized § 514.117(b)(3) as proposed.

D. Section 514.117(b)(4)

5. AHI commented that the list of acceptable study controls should not be ranked and the controls used should be ''appropriate to the scientific objectives of the study.'' AHI believes that justification for the use of each type of control is preferable to a ranking system that may erroneously give the impression that one type of control is always preferred over others.

FDA lists the acceptable types of controls in descending order, roughly in accordance with the ease of interpretation of the associated studies. Sponsors should not ascribe unintended meaning to the order in which the controls are listed. As discussed in the preamble to the proposed rule (62 FR 25153 at 25154), FDA believes that there may be good reasons for using different types of controls in study designs for particular situations and that the sponsor's choice of the type of control used in a particular study should be based on the scientific, ethical, and practical circumstances associated with that particular study. Therefore, the selection of the proper control is best addressed in discussions between FDA and the sponsor during protocol development.

6. AHI objected to FDA's inclusion in the preamble to the proposed rule of examples of when a specific type of control may not be appropriate. AHI asserted that humane considerations are always taken into account by the sponsor during the design phase of the study.

FDA did not include in the preamble examples of when specific types of controls may not be appropriate, rather FDA identified circumstances to be considered when choosing the type of control to be used in any particular study. An important consideration in choosing the type of control to be used is the humane treatment of the investigational animals, including control animals. FDA wanted to remind sponsors and the owners of investigational animals that considerations relating to the humane treatment of investigational animals require more than considering treatment versus no treatment. Notably, the use of an active control sometimes requires inducing a disease or condition in a greater number of animals than would be necessary with other types of controls, thus, a greater number of animals may suffer if the new animal drug proves to be unsafe or ineffective.

7. AHI believes that the proposed rule unfairly biases the value of active treatment controls. AHI noted that it is difficult, if not impossible, to find clinicians or owners who will allow studies conducted on an owner's animals with a placebo or no treatment. AHI noted further that the proposed rule implies that the only active controls that may be used are those drugs that have been tested in placebo-controlled studies. AHI objected to any limitation on the use of an approved drug as an active control, regardless of how it was approved, i.e., without data from a study with a placebo control.

It is not FDA's intent to express a bias against studies using active treatment controls. The overriding principle to be followed in selecting a type of control is to select a control that is appropriate to the scientific, ethical, and practical circumstances associated with the particular study. However, from a scientific standpoint, a demonstration of effectiveness by means of showing similarity of the new animal drug to an active control drug is an indirect demonstration of effectiveness and necessarily involves making assumptions that do not need to be made in studies with controls that permit a direct demonstration of effectiveness. For example, it must be presumed that the active control would have been superior to a placebo if there had been a comparison. Thus, if the particular circumstances of a study do not dictate a need for an active control, it is usually easier to interpret the results of studies using placebo or untreated controls.

It is understandable that clinicians and owners of investigational animals, including control animals, may be reluctant to participate in studies using placebo or untreated controls when a new animal drug is intended to cure, mitigate, treat, or prevent disease. Nonetheless, it is up to the sponsor to select, based on the particular circumstances of the study, the appropriate control and to obtain the informed consent of each owner who authorizes the use of their animal in the study.

In those instances in which a new animal drug is intended to affect the structure or function of the animal's body by increasing feed efficiency or weight gain (production animal drugs), it is much less clear why clinicians or owners would object to the participation of animals in studies using placebo or untreated controls, because there is no potential for animal suffering if the new animal drug is not administered or applied to the particular animal. In fact, the health of an animal could be compromised by the administration or application of the new animal drug if there are side effects from the investigational use of the new animal drug. Furthermore, because the effects of production animal drugs are generally small, they are more difficult to measure, and it can be expected that even active drugs will not prove effective in all studies. Studies involving placebo or untreated controls may be the only way to evaluate such treatments.

Use of active treatment controls in studies to evaluate the effectiveness of a production animal drug are likely to require the participation of a very large number of animals if, indeed, such controls are credible at all. In any instance in which a sponsor chooses to use an active treatment control, the sponsor should justify the need to use such a control.

Because comparison with an active treatment control establishes only that the new animal drug is more or less effective than, or as effective as, the active control, before FDA can evaluate the study FDA must know that the active treatment control is effective. One way, but not the only way, to provide information to FDA about the effectiveness of the active treatment control is to reference previous placebo-controlled studies of the active control drug. When such studies are not available, a sponsor should justify the choice of active treatment control and explain how it can be known that the active control drug was effective in the study.

E. Section 514.117(b)(5)

8. Proposed § 514.117(b)(5) would require that adequate and well-controlled studies use a method of selecting animals that provides adequate assurances that the animals are suitable for the purposes of the study. AHI believes that examples cited in the characteristic are too specific for inclusion in a regulation and should be eliminated. AHI notes that criteria for selection should be established on a case-by-case basis during the protocol review.

FDA does not agree that the examples provided in proposed § 514.117(b)(5) are too specific. The examples represent generally some of the criteria to be considered in selecting animals. The examples are drawn from, and clarify FDA's interpretation of, current § 514.111(a)(5)(ii)(*a*)(*2*)(*i*). FDA agrees that the criteria for selecting animals suitable for a study should be determined on a case-by-case basis during protocol development and nothing in the examples precludes such case-by-case determination.

F. Section 514.117(b)(6)

9. AHI believes that FDA has expanded the ''pertinent variables'' used to judge whether experimental units of animals are comparable and that such expansion is unnecessary.

The only difference in the list of pertinent variables described in proposed § 514.117(b)(6) from those variables listed in current § 514.111(a)(5)(ii)(*a*)(*2*)(*iii*) is the use of the phrase ''class of animal'' in place of the term ''species'' and the listing of ''dietary management'' and ''level of animal production'' in place of ''management practices.'' These substitutions represent a clarification, not expansion, of the list of variables. FDA is retaining § 514.117(b)(6) as proposed.

G. Section 514.117(b)(7)

10. AHI has asked for clarification of how FDA is interpreting the phrase ''analysts of the data'' under § 514.117(b)(7).

As used in proposed § 514.117(b)(7), ''observers'' of data refers to those individuals who, on behalf of the investigator or sponsor, observe, collect, or record data and information as part of the conduct of an adequate and well-controlled study. This would include individuals who analyze specimens and samples (including the new animal drug and animal feed bearing or containing the new animal drug) which are collected as part of such a study. In contrast, ''analysts'' of data refers to those individuals who, on behalf of the sponsor or investigator, analyze the data and information collected and recorded during the conduct of an adequate and well-controlled study. Both observers and analysts of the data would be expected to perform their functions in a manner which minimizes bias. For example, observers of the data should be ''blinded'' or ''masked'' at all times, while analysts of the data should maintain such ''blinding'' or ''masking'' as long as reasonable or practical.

H. Data Variations

11. AHI recommended that the definition of adequate and well-controlled studies include a new subsection entitled ''Data variations'' to explain that nonsystematic errors or omissions generally will not disqualify a study as being adequate and well controlled for purposes of establishing that a drug is effective for use as described in the proposed labeling. Data variations would be subject to review and would require an explanation.

FDA does not find it necessary to create a provision to address data variations. FDA has not, nor does FDA intend to, disqualify studies as not being adequate and well controlled based solely on a finding of nonsystematic errors or omissions, i.e., random human error, that are explained and do not affect the integrity of the study. Furthermore, sponsors may ask the Director of CVM to waive the requirement to meet a specific characteristic of an adequate and well-controlled study with respect to a specific study and still accept that study as an adequate and well-controlled study.

I. Uncontrolled Studies

12.As discussed in section II.B.1 of this document, proposed § 514.117(d), which describes how uncontrolled studies would be considered by FDA, has been redesignated in this final rule as § 514.117(e). FDA and the Coalition agree that regardless of the differences between field and laboratory studies, a control group (placebo, untreated, active treatment, or historical) is always needed for a laboratory or a field study to be an adequate and well-controlled study (see Memorandum of July 11, 1997, meeting with the Coalition for Animal Health, at 2, Docket No. 97N–0141). Not only is a study without a control group not acceptable as the sole basis for the approval of claims of effectiveness, such a study does not permit scientific evaluation of claims of effectiveness. Accordingly, the phrase ''including studies for which the Director has granted a waiver under paragraph (c) of this section, of the use of any necessary control described in paragraph (b)(4) of this section,'' in the first sentence in proposed § 514.117(d) was erroneous. FDA is revising § 514.117(e) to remove this phrase. Thus, § 514.117(e) is the same as current § 514.11(a)(5)(ii)(c).

J. Quality Assurance

13. AHI inquired whether reference to a ''documented quality assurance process or program'' is a reference to a quality assurance function and not a specific, defined quality assurance unit as required in 21 CFR 58.35.

In the preamble to the proposed rule (62 FR 25153 at 25155), FDA stated that it believes that generation of reliable data and information can best be accomplished by conducting adequate and well-controlled studies under a documented program of quality assurance. FDA is primarily concerned that sponsors develop and implement a quality assurance process that is carried out in accordance with the well-established principles of quality assurance. A well-established principle of quality assurance is that personnel responsible for quality assurance should be independent from those personnel responsible for the development of new animal drugs, including the conduct and monitoring of the study. Personnel responsible for quality assurance may or may not function as a ''unit.''

III. Environmental Impact

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.

IV. 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 following analysis demonstrates that the final rule is not an economically significant regulatory action as defined by the Executive Order and is consistent with the regulatory philosophy and principles identified in the Executive Order.

Section 2(e) of the ADAA requires FDA 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. Discussions between FDA and regulated industry during the development of the ADAA made it clear that the regulated industry is concerned that certain

scientific principles and practices may be difficult to apply in testing new animal drugs under actual field conditions. FDA reviewed the essentials of adequate and well-controlled studies currently identified in § 514.111(a)(5)(ii) and determined that these essentials continue to represent scientifically sound principles governing the conduct of adequate and well-controlled studies, whether conducted under laboratory or field conditions. However, FDA determined that the practices followed in the conduct of adequate and well-controlled studies in the target animal under field conditions may need to be more flexible in some regards than practices followed under laboratory conditions.

In its proposed rule published in the May 8, 1997, **Federal Register**, FDA proposed to amend its regulations in part 514 to further define the term ''adequate and well-controlled studies'' to allow for more flexibility in the practices followed in the conduct of adequate and well-controlled studies in the target animal under field conditions. Specifically, FDA proposed to incorporate by reference GSP's, that is, the practices to be followed in conducting studies in target animals under field conditions.

FDA received several letters from industry groups commenting on the proposed definition of ''adequate and well-controlled studies.'' Some of the comments criticized the rule for its failure to explicitly address the difference between field and laboratory studies and objected to FDA's reference to GSP's. In response to these comments, FDA has removed the references to GSP's and added language to the rule that will more explicitly address the differences between field and laboratory studies.

The definition of adequate and well-controlled studies has significance only within the context of the regulations governing investigational use and approval of new animal drugs. Because FDA has issued neither revised new animal drugs for investigational use regulations nor revised new animal drug applications regulations, there will be little or no effect on the level of effort expended by industry in testing the effectiveness of new animal drugs as part of the animal drug approval process. FDA did not receive any comments on its estimate of impacts for the proposal, which reached an identical conclusion. The agency notes that a thorough economic analysis will be conducted on the impact of proposed changes to the regulations governing investigational use new animal drugs and to the new animal drug application regulations in future proposals.

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 final 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 final rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

V. 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 issuing any final 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 final 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.

Lists 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 514.111 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 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 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.

* * * * *

3. New § 514.117 is added to subpart B to read as follows:

§ 514.117 Adequate and well-controlled studies.

(a) *Purpose*. The primary purpose of conducting adequate and well-controlled studies of a new animal drug is to distinguish the effect of the new animal drug from other influences, such as spontaneous change in the course of the disease, normal animal production performance, or biased observation. One or more adequate and well-controlled studies are required to establish, by substantial evidence, that a new animal drug is effective. The characteristics described in paragraph (b) of this section have been developed over a period of years and are generally recognized as the essentials of an adequate and well-controlled study. Well controlled, as used in the phrase adequate and well controlled, emphasizes an important aspect of adequacy. The Food and Drug Administration (FDA) considers these characteristics in determining whether a study is adequate and well controlled for purposes of section 512 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360b). Adequate and well-controlled studies, in addition to providing a basis for determining whether a new animal drug is effective, may also be relied upon to support target animal safety. The report of an adequate and well-controlled study should provide sufficient details of study design, conduct, and analysis to allow critical evaluation and a determination of whether the characteristics of an adequate and well-controlled study are present.

(b) *Characteristics*. An adequate and well-controlled study has the following characteristics:

(1) The protocol for the study (protocol) and the report of the study results (study report) must include a clear statement of the study objective(s).

(2) The study is conducted in accordance with an appropriate standard of conduct that addresses, among other issues, study conduct, study personnel, study facilities, and study documentation. The protocol contains a statement acknowledging the

applicability of, and intention to follow, a standard of conduct acceptable to FDA. The study report contains a statement describing adherence to the standard.

(3) The study is conducted with a new animal drug that is produced in accordance with appropriate manufacturing practices, which include, but are not necessarily limited to, the manufacture, processing, packaging, holding, and labeling of the new animal drug such that the critical characteristics of identity, strength, quality, purity, and physical form of the new animal drug are known, recorded, and reproducible, to permit meaningful evaluations of and comparisons with other studies conducted with the new animal drug. The physical form of a new animal drug includes the formulation and physical characterization (including delivery systems thereof, if any) of the new animal drug as presented to the animal. The protocol and study report must include an identification number which can be correlated with the specific formulation and production process used to manufacture the new animal drug used in the study.

(4) The study uses a design that permits a valid comparison with one or more controls to provide a quantitative evaluation of drug effects. The protocol and the study report must describe the precise nature of the study design, e.g., duration of treatment periods, whether treatments are parallel, sequential, or crossover, and the determination of sample size. Within the broad range of studies conducted to support a determination of the effectiveness of a new animal drug, certain of the controls listed below would be appropriate and preferred depending on the study conducted:

(i) *Placebo concurrent control.* The new animal drug is compared with an inactive preparation designed to resemble the new animal drug as far as possible.

(ii) *Untreated concurrent control.* The new animal drug is compared with the absence of any treatment. The use of this control may be appropriate when objective measurements of effectiveness, not subject to observer bias, are available.

(iii) *Active treatment concurrent control.* The new animal drug is compared with known effective therapy. The use of this control is appropriate when the use of a placebo control or of an untreated concurrent control would unreasonably compromise the welfare of the animals. Similarity of the new animal drug and the active control drug can mean either that both drugs were effective or that neither was effective. The study report should assess the ability of the study to have detected a difference between treatments. The evaluation of the study should explain why the new animal drugs should be considered effective in the study, for example, by reference to results in previous placebo-controlled studies of the active control.

(iv) *Historical control.* The results of treatment with the new animal drug are quantitatively compared with experience historically derived from the adequately documented natural history of the disease or condition, or with a regimen (therapeutic, diagnostic, prophylactic) whose effectiveness is established, in comparable animals. Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances. Examples include studies in which the effect of the new animal drug is self-evident or studies of diseases with high and predictable mortality, or signs and symptoms of predictable duration or severity, or, in the case of prophylaxis, predictable morbidity.

(5) The study uses a method of selecting animals that provides adequate assurances that the animals are suitable for the purposes of the study. For example, the animals can reasonably be expected to have animal production characteristics typical of the class(es) of animals for which the new animal drug is intended, there is adequate assurance that the animals have the disease or condition being studied, or, in the case of prophylactic agents, evidence of susceptibility and exposure to the condition against which prophylaxis is desired has been provided. The protocol and the study report describe the method of selecting animals for the study.

(6) The study uses a method to assign a treatment or a control to each experimental unit of animals that is random and minimizes bias. Experimental units of animals are groups of animals that are comparable with respect to pertinent variables such as age, sex, class of animal, severity of disease, duration of disease, dietary regimen, level of animal production, and use of drugs or therapy other than the new animal drug. The protocol and the study report describe the method of assignment of animals to an experimental unit to account for pertinent variables and method of assignment of a treatment or a control to the experimental units. When the effect of such variables is accounted for by an appropriate design, and when, within the same animal, effects due to the test drug can be obtained free of the effects of such variables, the same animal may be used for both the test drug and the control using the controls set forth in paragraph (b)(4) of this section.

(7) The study uses methods to minimize bias on the part of observers and analysts of the data that are adequate to prevent undue influences on the results and interpretation of the study data. The protocol and study report explain the methods of observation and recording of the animal response variables and document the methods, such as ''blinding'' or ''masking,'' used in the study for excluding or minimizing bias in the observations.

(8) The study uses methods to assess animal response that are well defined and reliable. The protocol and study report describe the methods for conducting the study, including any appropriate analytical and statistical methods, used to collect and analyze the data resulting from the conduct of the study, describe the criteria used to assess response, and, when appropriate, justify the selection of the methods to assess animal response.

(9) There is an analysis and evaluation of the results of the study in accord with the protocol adequate to assess the effects of the new animal drug. The study report evaluates the methods used to conduct, and presents and evaluates the results of, the study as to their adequacy to assess the effects of the new animal drug. This evaluation of the results of the study assesses, among other items, the comparability of treatment and control groups with respect to pertinent variables and the effects of any interim analyses performed.

(c) *Field studies.* (1) Field conditions as used in this section refers to conditions which closely approximate the conditions under which the new animal drug, if approved, is intended to be applied or administered.

(2) Studies of a new animal drug conducted under field conditions shall, consistent with generally recognized scientific principles and procedures, use an appropriate control that permits comparison, employ procedures to minimize bias, and have the characteristics generally described in paragraph (b) of this section. However, because field studies are conducted under field conditions, it is recognized that the level of control over some study conditions need not or should not be the same as the level of control in laboratory studies. While not all conditions relating to a field study need to be or should be controlled, observations of

the conditions under which the new animal drug is tested shall be recorded in sufficient detail to permit evaluation of the study. Adequate and well-controlled field studies shall balance the need to control study conditions with the need to observe the true effect of the new animal drug under closely approximated actual use conditions.

(d) *Waiver.* The Director of the Center for Veterinary Medicine (the Director) may, on the Director's own initiative or on the petition of an interested person, waive in whole or in part any of the criteria in paragraph (b) of this section with respect to a specific study. A petition for a waiver is required to set forth clearly and concisely the specific criteria from which waiver is sought, why the criteria are not reasonably applicable to the particular study, what alternative procedures, if any, are to be, or have been employed, and what results have been obtained. The petition is also required to state why the studies so conducted will yield, or have yielded, substantial evidence of effectiveness, notwithstanding nonconformance with the criteria for which waiver is requested.

(e) *Uncontrolled studies.* Uncontrolled studies or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness or target animal safety. Such studies, carefully conducted and documented, may provide corroborative support of adequate and well-controlled studies regarding effectiveness and may yield valuable data regarding safety of the new animal drug. Such studies will be considered on their merits in light of the characteristics listed here. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered.

Dated: February 25, 1998.

William B. Schultz,

Deputy Commissioner for Policy.

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DEPARTMENT OF THE TREASURY

Internal Revenue Service

26 CFR Part 1

[TD 8765]

RIN 1545–AL24; 1545–AS68

Change From Dollar Approximate Separate Transactions Method of Accounting (DASTM) to the Profit and Loss Method of Accounting/Change From the Profit and Loss Method to DASTM

AGENCY: Internal Revenue Service (IRS), Treasury.

ACTION: Final regulations.

SUMMARY: This document contains final Income Tax Regulations relating to adjustments required when a qualified business unit (QBU) that used the profit and loss method of accounting (P&L) in a post-1986 year begins to use the dollar approximate separate transaction method of accounting (DASTM) and adjustments required when a QBU that used DASTM begins using P&L. The regulations provide rules for taxpayers to construct an opening dollar balance sheet for the QBU and require income adjustments in certain cases.

DATES: These regulations are effective April 6, 1998.

FOR FURTHER INFORMATION CONTACT: Howard Wiener at (202) 622–3870 (not a toll-free number) of the office of Chief Counsel (International) within the Office of Chief Counsel, Internal Revenue Service, 1111 Constitution Avenue, N.W. Washington, DC 20224.

SUPPLEMENTARY INFORMATION:

Background

On January 5, 1993 and July 25, 1994, the IRS published proposed amendments to § 1.985–7 in the **Federal Register** at 58 FR 300 (INTL–0045–92) and § 1.985–1 in the **Federal Register** at 59 FR 37733 (INTL–0066–92), respectively. No public hearing was held and few comments were received. After consideration of these comments, the regulations are adopted as a Treasury Decision with modifications as described below.

Explanation of Provisions

I. Proposed Rules for Changing From P&L to DASTM (§ 1.985–7)

1. The Proposed Regulations

The proposed regulations under § 1.985–7 set forth transition rules for QBUs changing from the profit and loss method of accounting (P&L) to DASTM in tax years after 1987. Section 1.985–6 provides the translation rules for QBUs using DASTM in 1987. Generally, when a QBU changes its functional currency, two basic issues arise: (1) How should the QBU translate its balance sheet accounts into the new functional currency in a way that preserves any unrecognized currency gain or loss which accrued in the old functional currency; and (2) whether income adjustments need to be made to recognize any currency gain or loss which accrued in the old functional currency that cannot be preserved.

Section 1.985–5 provides rules that generally apply when a QBU changes its functional currency. Under § 1.985–5 balance sheet accounts are translated using the spot rate on the last day prior to the taxable year of change. In addition, § 1.985–5 generally requires recognition of unrealized exchange gain or loss on instruments and other accounts that were maintained in the functional currency to which the QBU is changing.

The proposed regulations issued under § 1.985–7 were issued in response to taxpayer comments that § 1.985–5 resulted in significant distortions when a QBU either elected or was required to use DASTM. Applying the spot rate on the last day prior to the year in which the QBU begins to use DASTM (the ''taxable year of change'') to translate fixed assets typically results in a significant loss of basis in dollar terms and does not take into account certain income and expense distortions that occur in the period immediately preceding the taxable year of change.

In response to taxpayers' comments, the proposed regulations provide for use of the translation rules provided under § 1.985–3. These rules generally translate fixed assets at the historical exchange rate and other assets and liabilities at the current exchange rate. To correct for distortions that would result from applying historic exchange rates for fixed assets while applying the current year's spot rate for other balance sheet accounts, the proposed regulations provide for income adjustments in the case of a controlled foreign corporation (CFC) and a branch that reflect amounts that would have been included in income under DASTM.

In the case of a CFC, the proposed regulations provide for a shareholder level income adjustment to the extent subpart F income realized during the period after 1986 until the taxable year of change differs from subpart F income that would have been realized if the CFC had used DASTM throughout this period. In the case of a branch, the regulations provide that any difference between the branch's local currency