

under section 512(l)(1) or (m)(5)(A) of the act, or the applicant has refused to permit access to, or copying, or verification of, such records as required by section 512(l)(2) or (m)(5)(B) of the act; or

(2) That on the basis of new information before him evaluated together with the evidence before him when the application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of such drug or animal feed are inadequate to assure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of; or

(3) That on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the labeling of such drug or animal feed, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of.

(d) Approval of an application pursuant to section 512(c) or (m)(2) of the act will be withdrawn on the basis of a request for its withdrawal submitted in writing by a person holding an approved new animal drug application on the grounds that the drug subject to such application is no longer being marketed and information is included in support of this finding, provided none of the conditions cited in paragraphs (a), (b), and (c) of this section pertain to the subject drug. A written request for such withdrawal shall be construed as a waiver of the opportunity for a hearing as otherwise provided for in this section. Withdrawal of approval of an application under the provisions of this paragraph shall be without prejudice.

(e) On the basis of the withdrawal of approval of an application for a new animal drug approved pursuant to section 512(c) of the act, the regulation published pursuant to section 512(i) of the act covering the conditions of use of such drug as provided for in the application shall be revoked. An application providing for the manufacture of

animal feeds bearing or containing such drug and approved pursuant to section 512(m)(2) of the act shall be deemed as withdrawn upon publication in the FEDERAL REGISTER of the order revoking the corresponding regulation.

[40 FR 13825, Mar. 27, 1975, as amended at 50 FR 7517, Feb. 22, 1985]

§ 514.116 Notice of withdrawal of approval of application.

When an approval of an application submitted pursuant to section 512 of the act is withdrawn by the Commissioner, he will give appropriate public notice of such action by publication in the FEDERAL REGISTER.

§ 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 as-

sess 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.

[63 FR 10770, Mar. 5, 1998]

EFFECTIVE DATE NOTE: At 63 FR 10770, Mar. 5, 1998, § 514.117 was added, effective Apr. 6, 1998.

§ 514.120 Revocation of order refusing to approve an application or suspending or withdrawing approval of an application.

The Commissioner, upon his own initiative or upon request of an applicant stating reasonable grounds therefor and if he finds that the facts so require, may issue an order approving an application that previously has had its approval refused, suspended, or withdrawn.

§ 514.121 Service of notices and orders.

All notices and orders under this subchapter E and section 512 of the act pertaining to new animal drug applications shall be served:

(a) In person by any officer or employee of the Department designated by the Commissioner; or

(b) By mailing the order by certified mail addressed to the applicant or respondent at his last known address in

the records of the Food and Drug Administration.

Subpart C—Hearing Procedures

§ 514.200 Contents of notice of opportunity for a hearing.

(a) The notice to the applicant of opportunity for a hearing on a proposal by the Commissioner to refuse to approve an application or to withdraw the approval of an application will specify the grounds upon which he proposes to issue his order. On request of the applicant, the Commissioner will explain the reasons for his action. The notice of opportunity for a hearing will be published in the FEDERAL REGISTER and will specify that the applicant has 30 days after issuance of the notice within which he is required to file a written appearance electing whether:

(1) To avail himself of the opportunity for a hearing; or

(2) Not to avail himself of the opportunity for a hearing.

(b) If the applicant fails to file a written appearance in answer to the notice of opportunity for hearing, his failure will be construed as an election not to avail himself of the opportunity for the hearing, and the Commissioner without further notice may enter a final order.

(c) If the applicant elects to avail himself of the opportunity for a hearing, he is required to file a written appearance requesting the hearing within 30 days after the publication of the notice, giving the reason why the application should not be refused or should not be withdrawn, together with a well-organized and full-factual analysis of the clinical and other investigational data he is prepared to prove in support of his opposition to the Commissioner's proposal. A request for a hearing may not rest upon mere allegations or denials, but must set forth specific facts showing there is a genuine and substantial issue of fact that requires a hearing. When it clearly appears from the data in the application and from the reasons and a factual analysis in the request for the hearing that no genuine and substantial issue of fact precludes the refusal to approve the application or the withdrawal of