

event listed on the labeling, but differs from the event because of greater severity or specificity. For example, under this definition hepatic necrosis would be unexpected if the labeling referred only to elevated hepatic enzymes or hepatitis.

[68 FR 15365, Mar. 31, 2003, as amended at 69 FR 51170, Aug. 18, 2004]

#### § 514.4 Substantial evidence.

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

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

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

(i) *Dose range labeling.* Sponsors should, to the extent possible, provide for a dose range because it increases the utility of the new animal drug by providing the user flexibility in the selection of a safe and effective dose. In general, substantial evidence to support dose range labeling for a new animal drug intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease must consist of at

least one adequate and well-controlled study on the basis of which qualified experts could fairly and reasonably conclude that the new animal drug will be effective for the intended use at the lowest dose of the dose range suggested in the proposed labeling for that intended use. Substantial evidence to support dose range labeling for a new animal drug intended to affect the structure or function of the body of an animal generally must consist of at least one adequate and well-controlled study on the basis of which qualified experts could fairly and reasonably conclude that the new animal drug will be effective for the intended use at all doses within the range suggested in the proposed labeling for the intended use.

(ii) [Reserved]

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

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

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

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

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

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

#### § 514.4

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

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

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

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

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

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

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

(C) That the active ingredients or animal drugs are physically compatible

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

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

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

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

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

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

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

[64 FR 40756, July 28, 1999]