

SECTION II

CLINICAL TRIALS--EXPERIMENTAL DESIGN

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Classification of Over-The-Counter and Prescription Drugs^a

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1. Purpose:

This guide outlines the process necessary to determine whether adequate directions for the safe and effective use of a drug product can be written for the layman; or whether, because of the nature of the drug and the particular label, an exemption for prescription legend labeling should be required.

2. Authority:

a. Federal Food, Drug, and Cosmetic Act:

- (1) Section 502(f)(1) - A drug or device shall be deemed to be misbranded unless its labeling bears adequate directions for use. (Provided the Secretary has not promulgated regulations exempting such drug or device from such requirements.)
- (2) Section 512(d)(2) - Relevant factors to be considered in determining whether a drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling.

b. Code of Federal Regulations:

- (1) 21 CFR 201.5 - Defines adequate directions for use.
- (2) 21 CFR 201.105 - Exempts from adequate directions for use veterinary drugs for which such directions cannot be written and which bear the prescription legend.

3. General Classification Considerations:

- a. The primary basis for distinguishing Rx and OTC animal drug products under the Act and the regulations is the ability (or lack of ability in the case of Rx products) to prepare "adequate directions for use" which would allow persons other than licensed veterinarians to use the product safely and effectively. In effect, the system establishes, when appropriate, a method of control that assures to a great degree that the Rx product ultimately gets into the hands of persons trained to use the product (i.e., the licensed veterinarian or the non-veterinarian whom the licensed veterinarian has determined is capable of using the product). Products for which adequate

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directions for use can be written for the layman must be labeled for over-the-counter (OTC) use. In determining whether directions for use are adequate, an important point for consideration is whether it is reasonably certain the conditions of use prescribed, recommended or suggested in the proposed labeling will be followed in practice, Sec. 512(d)(2)(D) and 21 CFR §514.111(a)(4)(iv).

- b. Safe use includes safety to the animal, safety of food products derived from the animals, safety to the person administering the drug, safety to persons associated with the animal, and safety in terms of the drug's impact on the environment.
- c. Effective use of a drug product assumes that an accurate diagnosis can be made with a reasonable degree of certainty, that the drug can be properly administered, and that the course of the disease can be followed so that an assessment can be made of the success or lack of success of the product in terms of its intended use. This assumption also implies that a timely adjustment can be made in the event that an expected effect is not seen.
- d. In the past, the same products used in varying routes of administration, dosage forms, and in varying species of animals may have been labeled "prescription" in one instance and non-prescription for other uses. The primary question is whether adequate directions for use can be written to assure safe and effective use. If an average food animal producer can safely and effectively administer a product, but a companion animal owner, regardless of label directions, cannot administer it safely and effectively, then the prescription status of the product must be different relative to these intended uses. If directions can be written for use for a particular route of administration (IV, IP, etc.) for one animal species, but not for another, it is not inconsistent to grant OTC status for the one use and require the Rx legend for the other.
- e. The length of a withdrawal period prior to slaughter or milk discard time may be considered, but that alone should not be used to determine Rx or OTC status. Each drug must be considered in light of the labeled use and characteristics of the drug, whether adequate directions can be written for the safe and effective use of the product, and whether it is reasonably certain the direction will be followed in practice.

4. Examples of Situations Requiring the Prescription Legend:

- a. Conditions of use of dichlorvos in swine are defined in 21 CFR 520.600(e). The product is required to be mixed with the feed and the amount for each size pig is specified. Under these conditions, the hog raiser is considered to be experienced enough

to intelligently administer the drug. The use of anthelmintics in dogs and horses, in some cases, requires such products to bear the prescription legend because the drug is given in a concentrated form. An example of this situation in horses is the use of dichlorvos in the feed compared to its use as a gel administered with a syringe. The dichlorvos placed on the feed is impregnated in plastic pellets (cut rod) and is released into the horse's body slowly during passage through the gastrointestinal tract. Adequate directions for the safe use of the drug in this manner can be written. The gel product is applied to the tongue, gums, and other areas of the oral region to kill embedded bot instars. This form is readily absorbed by the mucous membranes and, therefore, is more apt to cause an adverse reaction. Consequently, adequate directions for safe use by laymen cannot be written.

- b. The need to possess special skills to administer a drug product will also be a factor in determining whether it must bear the prescription legend. For example, while certain non-veterinarians may be able to effectively pass a stomach tube in certain species, many will not be able to do so and there is no practical way to write adequate directions for such use.
- c. The labeling of a vitamin preparation having claims for treatment of specific deficiencies and other medical/therapeutic indications may cause a product to carry a prescription legend. This is due to the difficulty of writing adequate directions for diagnosing these conditions by the laity. An example could be the difficulty of preparing directions for use of vitamin B₁₂ to treat a deficiency due to a lack of that specific vitamin.
- d. The Center's policy on synthetic and semi-synthetic penicillin products:
 - (1) Synthetic and semi-synthetic penicillins are required to carry the prescription legend, regardless of claims. This policy was developed several years ago as a result of concern by an FDA Advisory Committee about the development of resistant Staphylococcus in humans from potential widespread use of these drugs by the laity. This policy affects all the dosage form drugs used in veterinary medicine, including intramammary infusion products; and is generally understood as absolute by CVM personnel and industry. Exceptions to this requirement would be considered only if long term studies indicated no serious human or animal health hazard would exist from the emergence of resistant bacterial strains by the use of these agents in food producing animals.

- a. Intramammary infusion products (other than synthetic and semi-synthetic penicillins) are approved for OTC use basically when the products carry claims for both Staphylococcus aureus and Streptococcus agalactiae. These two organisms account for 95% of all cases of mastitis in cows. The Center's position has been to allow OTC labeling if both pathogens were shown to be eliminated by the drug or drug combination. This would be grounds for writing adequate directions for use since a specific diagnosis in the majority of cases would not be necessary prior to instituting treatment.

5. Guidance on Areas to be Considered:

Areas to be considered in deciding whether adequate directions for lay use can be written for an animal drug product:

a. Safety of the drug to the target animal:

- (1) Margin of Safety. Will minor overdose result in death, irreversible damage to the animal, disturbing reactions, prolonged unthriftiness in the animal?
- (2) Antidotes available to the veterinarian? To the layman? Can these be promptly and accurately administered by the veterinarian? By the layman?
- (3) Would one expect (certain) adverse reactions even when the product is used according to label? The severity of the reaction should be considered.
- (4) Would the layman be able to distinguish expected side effects from other signs of unrelated pathology in the animal?
- (5) What is the potential for serious problems due to interaction with other drugs, vaccines, pesticides, or foods?
- (6) Could misuse of the drug have the potential to promote a shift in disease characteristics or a change in the disease organism which might seriously affect the animal (e.g. development of drug resistant bacteria, immuno-suppression by steroidal agents, a change in intestinal flora)?
- (7) Is special handling necessary to insure humane treatment of the animal?

b. Safety to Man:

- (1) Could misuse of the drug mask or potentiate a disease communicable to man (e.g., treatment stopped too early)?

- (2) Could the misuse of the drug have the potential to promote a shift in disease characteristics or a change in the disease organism which might seriously affect man (e.g., drug resistant bacteria)?
- (3) Is there any danger to the person administering the product if it is not properly handled?
- (4) Would use of the Rx status significantly lessen (limit) an adverse impact on the quality of the environment?
- (5) Would inaccurate diagnosis or improper administration affect the safety of persons associated with the animal? How critical is the problem?
- (6) Would Rx status significantly increase likelihood of correct use and thereby assure safety of food derived from the target animal(s)?
- (7) Are the directions for use reasonably certain to be followed in practice?

c. Accuracy of Diagnosis:

- (1) Is the drug generally used for treatment of a readily recognized disease or is diagnosis difficult and possibly easily confused with other disease conditions?
- (2) Is it necessary that the signs of the disease be closely followed and adjustment of the treatment regime and dosage be made as dictated (e.g., heart disease and digitalization)?
- (3) Are facilities and equipment necessary for an accurate diagnosis available to the layman?

d. Nature of the Drug:

- (1) What is the potential for misuse in animals or man (e.g. prostaglandins for abortion in women)?
- (2) Is the drug a "controlled substance?" (DEA regulated, etc.)
- (3) Is it a new and untried entity? Would restriction to Rx status assist in timely notification of adverse reactions?

(4) Is special handling necessary? (special mixing, freezing, refrigeration, radioactive drugs, etc.).

(5) What is the route of administration? (IV, stomach tube, etc.)

NOTE: In the case of drug products proposed for OTC use, the drug sponsor should submit data demonstrating that the product can be safely and effectively used by the layman.

SAMPLE FOR PROTOCOL DEVELOPMENT*

During the process of protocol development, the following should be kept in mind:

1. What tests are adequate and reasonably applicable to show whether or not the new animal drug is safe and effective for use as suggested in the proposed labeling - 21 CFR 514.1(b)(8).
2. Reasons for which an application may not be filed - 21 CFR 514.110.
3. Reasons for which an application may be refused for approval - 21 CFR 514.111.

In general, the following should be included in a protocol for clinical (field) investigations for safety and efficacy:

1.0 STUDY OBJECTIVE

2.0 INVESTIGATORS

2.1 Principal Investigator

2.2 Investigator's Staff

2.3 Facilities

2.31 Name and address of clinic or institution

2.32 Name and address of bacteriology laboratory

2.33 Name and address of diagnostic laboratory

2.4 Clinic or Institutional Review

2.41 Name of committee members

3.0 EXPERIMENTAL PLAN

3.1 Patient Sample Characterization

3.11 Age

*Information Was Extracted from Various Industrial Protocols

- 3.12 Sex
- 3.13 Weight
- 3.14 Breed(s)
- 3.15 Number of animals
- 3.2 Source of Animals
- 3.3 Concurrent Diseases
 - 3.31 Those permitted
 - 3.32 Those not permitted
- 3.4 Concurrent Medication
 - 3.41 Those permitted
 - 3.42 Those not permitted
- 3.5 Criteria for Animal Admission to Study
 - 3.51 Informed consent of owner(s)
 - 3.52 Presence of disease condition to be studied
 - 3.521 Symptoms began within what time frame before being admitted to study
 - 3.512 Condition should be acute and not represent an isolated episode of a chronic condition - record number of previous episodes that have occurred during the past year
 - 3.523 Means by which the presence of the diseased condition will be determined
 - 3.53 Other (specify)
- 3.6. Exclusion Criteria
 - 3.61 Animal is known or suspected of having idiosyncratic or allergic potential to test drug

- 3.62 Recipient of previous medication
- 3.63 Patient with known complications that would compromise the study
- 3.64 Other (specify)

4.0 PROCEDURES

- 4.1 Formulations of Clinical Trial Materials (CTM)
- 4.2 Packaging, Labeling, and Dispensing of Clinical Trial Materials to Maintain Blinding of Study
 - 4.21 Packaging
 - 4.22 Dosage schedule
 - 4.23 Dispensing
- 4.3 Type of Study
 - 4.31 Single-blinded trial and procedure for blinding
 - 4.32 Double-blinded trial and procedure for blinding
- 4.4 Treatment Plan: The study will last up to _____ days per patient/group and will be divided into two parts:
 - 4.41 First part - drug therapy period
 - 4.42 Second part - observation period. This part of the study will continue up to days/months maximum after completion of therapy period.
 - 4.43 Follow-up evaluation
 - 4.431 Evaluation of subjects at end of therapy
 - 4.432 Days following therapy subjects are to be evaluated
 - 4.433 Tests to be employed in evaluation

- 4.44 Residual medication
 - 4.441 How is the residual medication to be disposed of
 - 4.442 Who will be the responsible individual
- 4.5 Bacteriological Cultures and Susceptibility Testing
 - 4.51 Instructions for taking cultures
 - 4.52 Cultures prior to initiation of therapy
 - 4.53 Cultures at conclusion of therapy
 - 4.54 Cultures _____ days following conclusion of therapy
 - 4.55 Handling of samples taken for culturing
 - 4.56 For what should the cultures be evaluated
 - 4.57 What drugs should be included in the sensitivity tests
- 4.6 Urine Collection - for Urinary Infections Only
 - 4.61 Instructions for taking samples
 - 4.62 Colony count _____ of bacteria/ml that would be considered as acceptable for significant bacteriuria
 - 4.63 Cultures prior to initiation of therapy
 - 4.64 Other tests to be performed on the urine samples
 - 4.65 Culture at conclusion of therapy
 - 4.66 Culture _____ days following conclusion of therapy
- 4.7 Samples for Hematology and Blood Chemistries
 - 4.71 Instructions for taking blood samples
 - 4.72 Hematology tests to be run
 - 4.73 Blood chemistry tests to be run

4.8 Dosages of Experimental and Control Drugs

- 4.81 Dosage: _____ mg/kg
- 4.82 Route of administration
- 4.83 Frequency of administration
- 4.84 Duration of therapy
- 4.85 Provisions for:
 - 4.851 Adverse effects
 - 4.852 Change of therapy if patient fails to respond to therapy within a given time (specify)

5.0 CLINICAL OBSERVATIONS

- 5.1 History and Physical Examination - Individual/Group Case Report
 - 5.11 Medication received during the past week
 - 5.12 Clinical signs of particular significance that patient should be checked for prior to initiating therapy
 - 5.13 Diary of patient during therapy
 - 5.14 Observations at conclusion of therapy
 - 5.15 Observations _____ days following conclusion of therapy
- 5.2 Response Scale to Evaluate Patient/Drug Efficacy
 - 5.21 Clinical cure
 - 5.22 Clinical improvement
 - 5.23 Clinical failure
- 5.3 Adverse Reactions
 - 5.31 How will adverse reactions be handled
 - 5.32 How will adverse reactions be evaluated as related to investigational drug

- 5.33 Circumstances for which the firm monitor should be notified immediately
- 5.4 How Will the Patients be Handled
 - 5.41 As in clinic patients
 - 5.42 As out-patients
- 5.5 Patient Withdrawal or Removal from Study
 - 5.51 Reasons why a patient may be withdrawn
 - 5.52 How will withdrawal be documented
- 6.0 PROCEDURAL TIMETABLE
- 7.0 DISCONTINUANCE OF STUDY
 - 7.1 Rights of firm to discontinue the study
 - 7.2 Deposit of residue drugs
 - 7.3 Notification of FDA/CVM
- 8.0 INSTRUCTIONS TO INVESTIGATORS
 - 8.1 Changes in Protocol
 - 8.11 Will changes be permitted
 - 8.12 If changes are permitted, how are they to be handled (written documentation)
 - 8.2 Use of Drug
 - 8.21 Only in the manner described in protocol
 - 8.3 Recording and Reporting of DATA
 - 8.31 Recording data
 - 8.311 All forms are to filled out completely
 - 8.312 Record data neatly and legibly in black ink
 - 8.313 Case report forms should be dated and signed by investigator(s)

8.32 Reporting data

8.321 Any serious or alarming reaction, including death due to any cause which occurs during the trial (whether related or not to the investigational drug) shall be reported immediately to the study monitor

8.322 Explanation will be given for any missing information

8.323 Investigator(s) shall summarize his/her data and write a summary of his/her conclusions

8.33 Retention of records (regulation requirements)

8.34 Drug return - how is it to be handled

8.341 Destroyed by investigator

8.342 Returned to sponsor

9.0 MONITORING OF THE STUDY

9.1 Investigator will allow a representative of the firm's monitoring team to inspect all clinical report forms at regular intervals throughout the study

9.2 Authorized FDA personnel will be granted the same privilege

9.3 These inspections are for the purpose of verifying the adherence to the protocol and the completeness and exactness of the data being entered on the clinical forms

10.0 PUBLICATIONS

10.1 Rights of the firm

10.2 Rights of the investigator(s)

11.0 STATISTICAL METHODS PROPOSED FOR USE IN ANALYSIS OF DATA