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**GENERAL REVIEW AND ENFORCEMENT POLICIES**

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**ADVERSE REACTIONS AS A BASIS FOR REGULATORY ACTION**

The nature of a regulatory agency requires that decisions must be made rapidly, accurately, and with purpose. New animal drug applications are approved, even under the best of conditions on partial information based on limited data and limited numbers of animals. Unexpected responses may occur in the field when an approved product is used on large numbers of animals and under varying conditions of use. There are no set formulas to follow in determining at what point adverse reactions or misbrandings become serious enough to require withdrawal from the market or other corrective action. Taking into consideration all known facts, decisions must be made.

I. Purpose:

This document outlines the general considerations and procedures recommended for evaluating situations for regulatory actions.

II. General:

- A. The review of reports (adverse reactions, advertising, establishment inspections, etc.) for the purpose of determining whether or not regulatory action is indicated, represents an important part of the activities of the Center for Veterinary Medicine. In order to prevent serious injuries, a decision should be reached as soon as possible. On the other hand, unjustified actions against valuable products, may deprive the public of useful drugs. It is necessary, therefore, that decisions be both rapid and correct.
- B. In evaluating adverse reactions in particular, it is necessary to attempt to develop a differential diagnosis just as is done with a client in regular veterinary medical practice. This should include possible effects of other drugs administered and possible symptoms and complications of any disease the animal is known or suspected to have.
- C. In evaluating other types of violative acts that are reported, a similar consideration of causes, extenuating circumstances, precedent, and potential for correction is needed.
- D. In many cases, reactions-even though real--are not of sufficient importance to require any changes in the labeling or composition of the drug. In other cases, changing of the full disclosure material to alert practitioners of the possibility of the reaction is sufficient and will be carried out voluntarily by the manufacturer. Where NADA administrative procedures are not applicable, the decision as to the actual mechanics to be used to bring about compliance with recommendations is made by the Center

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for Veterinary Medicine and with advice from the Office of the Chief Counsel as necessary.

- E. FDA actions are to be based on the best information available that will sustain a regulatory action; guesses and impressions alone are not enough. Premature publicity concerning investigations and adverse reactions is to be avoided.

### III. Significant Questions for Adverse Drug Reaction Cases:

Answers to the following questions will often resolve the proper course of compliance action:

- A. Is the reaction real?
1. Initially, it is necessary to determine if any reaction, adverse or otherwise, has actually taken place. A reaction is not necessarily false simply because it appears to be scientifically impossible nor is it necessarily true because it agrees with accepted scientific fact.
  2. Some reactions may represent misinterpretation of normal body processes, and are not drug-related adverse reactions.
- B. Is the reaction really a part of the normal course of the disease for which the drug was taken?
1. A distinction must be made between direct toxic effects (adverse reactions) and therapeutic ineffectiveness.
  2. To evaluate an adverse reaction, it is desirable to know as much as possible about the condition of the animal at the time the drug was administered. If adequate information is not given, the veterinarian involved should be contacted.
- C. Is the reaction due to an intercurrent disease?
- Animals may suffer from more than one disease simultaneously. Symptoms which are not due to the primary condition may be due to an unrelated disease process rather than a drug reaction. Age, sex, geographic location, etc., should all be considered in evaluating injury reports.
- D. Could the drug have caused the reaction?
1. It is obviously impossible to evaluate any preparation without knowing its composition. In many cases, the active ingredient is identified on the label

and the suspected reaction can readily be determined to be one of its well-known side effects. In other cases, the preparation may be unknown. If the complete composition is not obtainable from the NADA, a review of a recent establishment inspection may turn up the desired information.

2. Although fillers and other inactive ingredients are expected to be inactive, such compounds may produce allergic or other adverse effects in susceptible individuals.
3. Having determined the composition of the preparation in question and with details of the supposed adverse reaction, it may be possible to determine whether the reaction is actually related to the particular product administered.

#### IV. Types of Reactions:

Types of reactions may be classified according to the circumstances under which they occur.

- A. Direct action of the drug. This probably is the most frequent type of reaction and often may be anticipated from the known pharmacology of the preparation; however, new and unexpected reactions or reaction rates, higher than previously known, taking into consideration drug sales, may require revision of labeling or reconsideration of uses. A greater than expected frequency of "known reactions" may necessitate labeling changes to provide increased prominence to precautionary information.
- B. Action of the drug in abnormal metabolic states due to disease. Reactions of this type may require label revisions in the form of additional contraindications or special precautionary statement regarding use for certain disease conditions, certain age groups, etc.
- C. Unintentional misuse. Unintentional misuse may require Food and Drug Administration action if it appears that the labeling of the drug predisposes to such misuse.
- D. Deliberate misuse. For one reason or another, persons may intentionally use a product at doses other than those indicated on the label or for conditions other than those recommended. If such uses result in adverse effects, label warning may be necessary. If the manufacturer is promoting a product for these unapproved uses, then regulatory action against the firm or the NADA should be considered.
- E. Abuse. Drugs having a potential for abuse because of a depressant, stimulant, or hallucinogenic effect are subject to special controls under the Drug Enforcement Administration.

V. Supporting Evidence:

## A. Food and Drug Administration Sources:

1. In validating the reports of reactions, it is important to determine the pattern of occurrence. A small number of reports from widely-scattered sources may be of more value than a large group collected from a single source.
2. Information regarding both the pharmacology of drugs and treatment of various disease conditions should be sought first in readily-available sources such as DERs, pharmacology texts, U.S. Dispensatory, and the Merck Index.
3. Computer database and files on adverse reaction reports are available. If information is still insufficient to make a decision, it may be necessary to secure a literature search. Searches directed as closely as possible to the problem at hand are most productive of useful information.
4. In the event of serious regulatory problems, animal investigations can be carried out by Office of Research.

## B. Consultation:

1. Before undertaking interviews with experts in the field, it is best to review all available literature sources. Much more will be learned in the interviews if the veterinary medical officer is able to ask intelligent questions regarding the metabolic and physiological uses of the drug and is thoroughly conversant with the disease processes for which it is used.
2. For clinical opinions regarding the value of a drug for a particular condition, a recognized expert in one of the veterinary colleges may be consulted.
3. Clinical or animal studies may be done locally if time permits and facilities are available. Under exceptional circumstances, animal and clinical studies can be obtained through outside agencies such as private research groups and university affiliated research centers. Such studies are extremely time-consuming and, from the preliminary planning stages to completion, take from one to two years so that this approach is not suitable for acute or pressing problems.
4. If necessary or desirable, a national or world authority may be consulted for additional information.