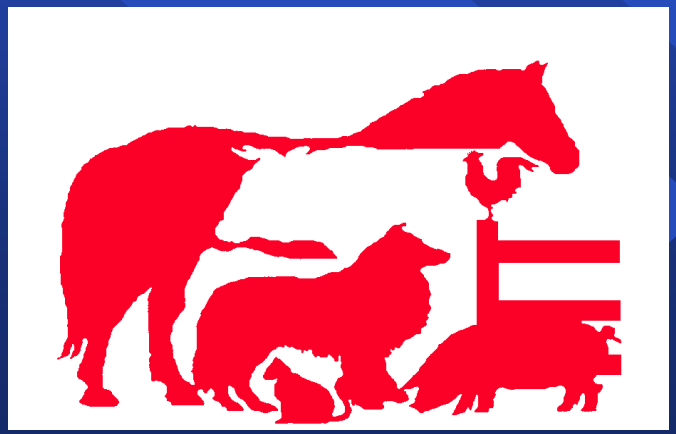
U.S. FOOD AND DRUG ADMINISTRATION

CENTER FOR VETERINARY MEDICINE

OFFICE OF NEW ANIMAL DRUG EVALUATION



OVERVIEW
of the
ANIMAL DRUG APPROVAL PROCESS

presented by

Steven D. Vaughn, D.V.M.
Director, Division of Therapeutic Drugs for Food Animals
Office of New Animal Drug Evaluation
Center for Veterinary Medicine

PRESENTATION TOPICS

- **Background Information - definitions & structure**
- **Investigational New Animal Drug Process**
- **NADA Technical Sections**
- **New Animal Drug Application Process**

BACKGROUND INFORMATION: DEFINITIONS AND STRUCTURE

- Federal Food, Drug, and Cosmetic Act (FFDCA)
- Definition of a new animal drug
- Section 512 of the FFDCA - New Animal Drug Applications
- Original, Supplemental, Generic Applications
- 512 (j) Investigational New Animal Drug Exemption (INAD)

BACKGROUND INFORMATION: DEFINITIONS AND STRUCTURE

- As mandated by the Federal Food, Drug and Cosmetic Act, a new animal drug may not be sold in interstate commerce unless it is the subject of a New Animal Drug Application (NADA).

BACKGROUND INFORMATION: DEFINITIONS AND STRUCTURE

- What does an approved NADA mean?
  - The product is safe and effective for its intended use.
  - The methods, facilities and controls used for the manufacturing, processing and packaging of the drug are adequate to preserve its identity, strength, quality and purity.

BACKGROUND INFORMATION: DEFINITIONS AND STRUCTURE

DEFINITION OF EFFECTIVENESS

- **Based on substantial evidence consisting of one or more adequate and well controlled investigations, such as -**

BACKGROUND INFORMATION: DEFINITIONS AND STRUCTURE

DEFINITION OF EFFECTIVENESS

- **a study in a target species**
- **a study in laboratory animals**
- **any field investigation***
- **a bioequivalence study**
- **an *in vitro* study**

BACKGROUND INFORMATION: DEFINITIONS AND STRUCTURE

DEFINITION OF EFFECTIVENESS

- **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.**

BACKGROUND INFORMATION: DEFINITIONS AND STRUCTURE
DEFINITION OF SAFETY

- **Adequate tests by all methods reasonably applicable show that the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling.**

BACKGROUND INFORMATION: DEFINITIONS AND STRUCTURE

SAFETY

- **Human Food Safety**
- **Target Animal Safety**
- **Environmental Safety**
- **User Safety**

BACKGROUND INFORMATION: DEFINITIONS AND STRUCTURE

HUMAN FOOD SAFETY

- Meat, milk and eggs
- Drug residues
  - Direct - acute toxic response
    - Chronic exposure toxicity
  - Indirect - antimicrobial resistance

BACKGROUND INFORMATION: DEFINITIONS AND STRUCTURE
TARGET ANIMAL SAFETY

- **The cumulative effect of the drug on the animal(s), such that the drug does not adversely affect the treated animal(s)**

BACKGROUND INFORMATION: DEFINITIONS AND STRUCTURE
ENVIRONMENTAL SAFETY

- **Use, manufacture and disposal does not pose a significant environmental impact as per NEPA, CWA, etc.**
- **NADA Approval includes either a Categorical Exclusion or an Environmental Assessment accompanied by FONSI, or EIS**

BACKGROUND INFORMATION: DEFINITIONS AND STRUCTURE
USER SAFETY

- Hazards associated with manufacturing
  - Direct - occupational exposure at site
  - Indirect - manufacturing emissions
- Hazards associated with administration to animals
- Hazards associated with use of air, water and solid wastes contaminated via use and disposal of the drug

BACKGROUND INFORMATION: DEFINITIONS AND STRUCTURE
NADA

- **Approved drug product consists of the drug, the packaging and the labeling**
- **NADA is a systematic approach to document evidence that drug products are safe and effective**

BACKGROUND INFORMATION: DEFINITIONS AND STRUCTURE
NADA

- **CVM describes the documented evidence in a Freedom of Information Summary, an Environmental Assessment, and in drug labeling.**
  - **All are accessible by the public**

BACKGROUND INFORMATION: DEFINITIONS AND STRUCTURE
NADA

- **Anyone can sponsor an NADA**
- **Usually pharmaceutical firms**
  - **monetary resources**

PRESENTATION TOPICS

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INVESTIGATIONAL NEW ANIMAL DRUG PROCESS
PRE-INAD

- **Pharmaceutical sponsor pre-INAD discovery research**
  - **Discovery of new molecules**
  - **Purchase of patented entities**
  - **Pilot studies**
    - **Pharmacologic value**
    - **Laboratory and target species**
    - **Dose, toxicity, and pharmacokinetic studies**

INVESTIGATIONAL NEW ANIMAL DRUG PROCESS
PRE-INAD

- **Pharmaceutical management decides on marketability of drug**
- **Drug enters product development phase based on need, economics, etc.**
- **During early drug development phase sponsor obtains an INAD from CVM**

INVESTIGATIONAL NEW ANIMAL DRUG PROCESS

INAD

- **CVM does not take the initiative to propose products and label indications**
- **Sponsors propose the drug product and label indications**
- **Sponsors conduct the necessary research to support drug safety and effectiveness**

INVESTIGATIONAL NEW ANIMAL DRUG PROCESS
INAD

- **Research conducted under an INAD exemption**
  - **Legal requirements are described in 21 CFR Part 511**
  - **Allows shipment of the investigational drug via interstate commerce to investigators**
  - **Allows authorization for the use of edible tissues from animals treated with the investigational drug**

INVESTIGATIONAL NEW ANIMAL DRUG PROCESS

INAD

- Research conducted under an INAD exemption (cont)
  - Allows for the conduct of studies to collect data and document safety and effectiveness of the investigational drug
  - Certain requirements for administering an INAD including labeling requirements, collection of data, maintenance of records, accountability of drug shipments, receipt and use, accountability of treated animals and their disposition, qualifications of investigators

INVESTIGATIONAL NEW ANIMAL DRUG PROCESS
INAD

- On a formal or voluntary basis
  - Sponsor and CVM discuss and agree on
    - Product Development Plan
    - Protocol for each study or use of a standard protocol
  - Pre-submission conference - formal process
- CVM provides guidance documents for various studies

INVESTIGATIONAL NEW ANIMAL DRUG PROCESS
INAD

- **Sponsor conducts studies to generate data following protocol**
- **Data is evaluated by sponsor and CVM for quality assurance (data integrity)**
- **Data is scientifically reviewed by CVM**
- **CVM determines if study is acceptable (pivotal) for making safety or effectiveness decision**

PRESENTATION TOPICS

- Background Information - definitions & structure
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TECHNICAL SECTIONS

- Public Safety: toxicology, residue chemistry, etc.
- Target Animal Safety
- Environmental Safety
- Effectiveness
- Manufacturing Chemistry

TECHNICAL SECTIONS
Public Safety - Toxicology, etc.

- **Mutagenicity Studies**
- **Two 90-Day Feeding Studies**
- **Reproductive Study**
- **Teratology Study**
- **Special Studies (as needed)**
- **User Safety Information**
- **Salmonella Shedding Study**
- **Resistance Study**

TECHNICAL SECTIONS

Public Safety

Residue chemistry & regulatory methods

- **Total metabolism in target animals**
- **Comparative metabolism in rodents**
- **Analytical methods**
- **Tissue residue depletion studies**
- **Method validation**

TECHNICAL SECTIONS
Target animal safety

- **Tolerance study**
- **Reproductive Safety Study**
- **Animal Class Safety Study (e.g., young, geriatric)**
- **Special Cases (specific breeds)**

TECHNICAL SECTIONS
Environmental

- **Categorical Exclusion or**
- **Environmental introduction and fate studies**
- **Environmental effects studies**
- **Environmental assessment**

TECHNICAL SECTIONS
Effectiveness

- **a study in a target species**
- **a study in laboratory animals**
- **any field investigation***
- **a bioequivalence study**
- **an *in vitro* study**

TECHNICAL SECTIONS
Manufacturing methods and controls

- **Methods and controls**
- **Stability data**

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NEW ANIMAL DRUG APPLICATION PROCESS

- Phased Review/Direct Review
- Composition of New Animal Drug Application - Form 356V
- Technical Section Complete Letters
- Environmental Assessment
- Freedom of Information Summary
- Labeling

MISCELLANEOUS TOPICS

- Bioresearch Monitoring (BIMO)
- Animal Drug Availability Act (ADAA)
- Professional Flexible Labeling (PFL)
- Minor Uses/Minor Species