Governance of VMPs: Legislation, registration, and distribution

Bettye K. Walters, DVM

U. S. Food and Drug Administration

Bettye.walters@fda.hhs.gov

Status of VMP Oversight globally

- There are some countries that have no significant regulatory programs for controlling veterinary medicines
- Some countries might have diffuse, non-harmonized controls at state or local levels
- Some countries *may* even have the need to identify a government focal point and build information-sharing networks

Basic Principle

- **All regulatory programs need a core set of scientific competencies to be in place, and standards and procedures need to be available and implemented to undertake data assessments and/or understand the assessments conducted by others.**

- Legislation is a ***key element***

General Principles of Veterinary Legislation OIE Terrestrial Health Code Chapter 3

- Respect for the hierarchy of Acts or Laws
- Legal basis
- Inventory of the veterinary legislation
- Communication
- Codification
- Consistency
- Participation in the process and consultation

Regulation of Animal Heath Across Government

Animal Drugs and Feeds:
Antimicrobials,
Antiparasiticides,
Production Drugs, Medicated Feeds

Veterinary Biologics:
Vaccines, Bacterins, Antisera,
Diagnostic Kits,
Other products of biological origin,
Animal products (meat, milk, liquid/dried/frozen eggs)

Pesticides:
Insecticides, Fungicides, Rodenticides

Hierarchy of legislation: US Example

- Law
  - Federal Food, Drug and Cosmetic Act (1938)
  - Virus, Serum, and Toxin Act (1913)
- Regulations - Code of Federal Regulations (CFR)
- Policies and Guidelines - Guidances

Competent Authority

OIE Terrestrial Health Code Chapter 3.4

- Legal authority to intervene
- Access to regulated premises and documents
- Taking of samples
- Seizure and retention
- Suspension of activities
- Temporary, partial or complete closure of establishments
- Suspension or withdrawal of authorisations or approvals

What should veterinary legislation ***provide***? OIE Terrestrial Health Code Chapter 3.4

- Veterinarians and veterinary para-professionals
  - Define minimum requirements and competencies
  - Role of veterinary statutory body
- Laboratories
  - Reference laboratories
  - Reagents

Veterinary Medicinal Products Legislation OIE Terrestrial Health Code Chapter 3.4

- Basis for Competent Authorities to meet their obligations for assuring the quality of VMPs and minimizing the risk to humans, animals, and the environment associated with their use.
  - OIE Terrestrial Animal Health Code
  - VICH Guidelines
  - Codex Alimentarius Commission
  - SPS Agreement

VMP Life span

OIE Terrestrial Health Code Chapter 3.4

1. Raw materials
2. Authorisation
3. Quality
4. Establishments producing, storing and wholesaling
5. Retailing, use, and traceability

General measures: VMPs

Article 3.4.11

- Definition of veterinary medicines and biologicals

- 21 Code of Federal Regulations (CFR)
  - **Section 510—Definition of a new animal drug**

    "any drug intended for use in animals other than man, including any drug intended for use in animal feed but not including the animal feed….."

US Example: Authorisation of Animal Drugs

- 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

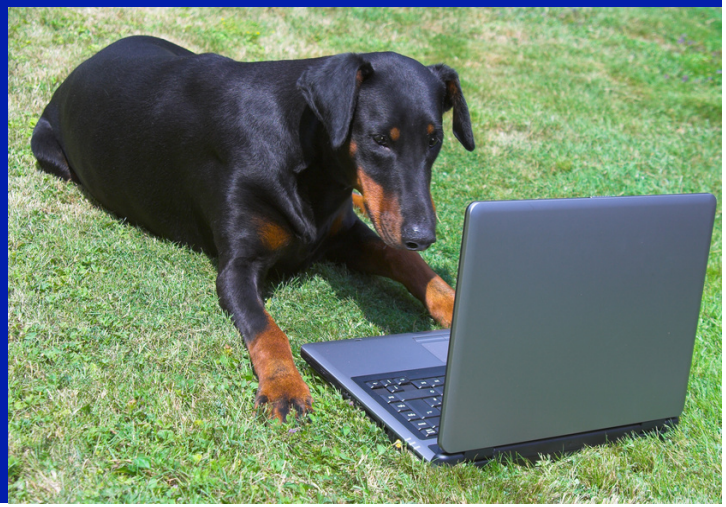
  - **An approved new animal drug application (NADA) under section 512 of the FFDCA**
  - **An approved abbreviated NADA under section 512 of the FFDCA**
  - **Minor Use / Minor Species (MUMS) drugs**
    - **A conditional approval under section 571 of the FFDCA or**
    - **An index listing under section 572 of the FFDCA**

Authorisation of Animal Drugs
US Example: Four Critical Standards

- Safety
  - Human Food
  - Target Animal
  - Environmental
  - User Safety
- Effectiveness - Substantial Evidence
- Quality Manufactured Product
- Properly Labeled Product

US Example: New Animal Drug Application Process

- Traditional New Animal Drug Application (NADA)
- Administrative New Animal Drug Application (NADA)
  - Phased review process



US Example: New Animal Drug Approval Process

Technical Sections

- Effectiveness
- Human Food Safety
- Target Animal Safety
- Environmental Safety
- Chemistry, Manufacturing and Controls
- Labeling and All Other Information (AOI)
- Freedom of Information (FOI) Summary

US Example: Effectiveness Technical Section

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

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

Safety

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

Technical Sections
Human Food Safety

- VICH GL 46, 47, 48, 49 Metabolism and residues of pharmaceutical products in food producing animals

- GUIDELINES FOR THE DESIGN AND IMPLEMENTATION OF NATIONAL REGULATORY FOOD SAFETY ASSURANCE PROGRAMME ASSOCIATED WITH THE USE OF VETERINARY DRUGS IN FOOD PRODUCING ANIMALS CAC/GL 71-2009

US Example: Technical Sections Human Food Safety

TOXICOLOGY:

- determine the no observable effects level (NOEL), acceptable daily intake (ADI), and safe concentration

RESIDUE CHEMISTRY:

- determine the target tissue, marker residue, slaughter withdrawal, and milk withhold times

MICROBIAL FOOD SAFETY:

- evaluate the safety of antimicrobials with regard to their microbiological effects on bacteria of human health concern (Guidances 152 and 159)

REGULATORY METHOD:

- development and validation of methods to measure drug residues in edible tissues

Technical Sections
Target Animal Safety

- The goals of target animal safety studies are to identify the toxic effects of the drug and establish a margin of safety for the labeled dosage regimen (dose, route, frequency, duration)
- Target animal safety studies are generally conducted in a small number of healthy animals
- An approval may not require multiple types of safety studies
- Safety information is also collected during the effectiveness studies and in review of All Other Information (AOI)
- VICH GL 43 Target Animal Safety Testing for Veterinary Pharmaceutical Products
- VICH GL 41 and 44 Target Animal Safety Testing veterinary biologicals

Technical Sections
Environmental Safety

Use, manufacture, and disposal does not pose a significant environmental impact

VICH GL 6 and 38

Technical Sections
User Safety

- Hazards associated with manufacturing
- Hazards associated with administration to animals
- Hazards associated with use of air, water and solid wastes contaminated via use and disposal of the drug

Technical Sections Manufacturing, Chemistry, and Controls

Determines whether an animal drug will have and maintain the necessary **quality, strength, purity,** and **identity**

- **Methods and controls**
- **Stability data**
- **GMP compliance**

Technical Sections
Manufacturing, Chemistry, and Controls

- How and where is the drug made?
- How are raw materials tested and monitored?
- What control procedures are in place to assure product consistency and quality?
- Are quality attributes adequately identified and characterized for the product?
- Are the test methods used to monitor product quality appropriate?
- How long does the product maintain its quality after it is made (shelf life)?


Flowchart linking the clinical studies to the drug marketed to consumers. The key is using the same processes and raw materials used to manufacture the clinical batch.
Drug used in clinical studies
Safe and effective
The same (or similar) processes and raw materials should be used to manufacture the drug used in clinical studies and the marketed drug
Drug marketed to consumers
Commercial product

Review of the CMC information helps assure that the same or similar processes are used

Clinical Batches
Safety and effectiveness studies

Pilot Batches
CMC information

Engineering Batches
Scale-up from pilot to commercial

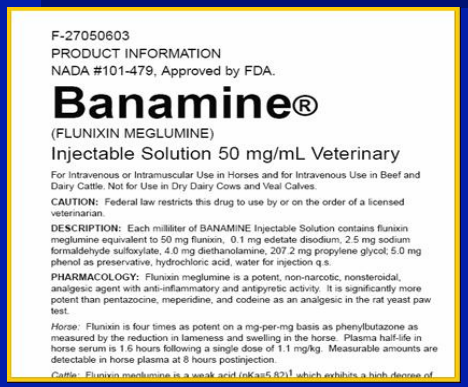
Process Validation Batches
Implementation of commercial manufacturing processes

Commercial Batches
Product marketed to consumers

These batches should be made using the same or similar processes and raw materials

Technical Sections
Labeling and AOI

- immediate container (vial, dosing syringe, packet, drum) or feed bag labels
- package insert
- packaging (box, carton)
- shipping label



F-27050603
PRODUCT INFORMATION
NADA #101-479, Approved by FDA.

Banamine®
(FLUNIXIN MEGLUMINE)
Injectable Solution 50 mg/mL Veterinary

For Intravenous or Intramuscular Use in Horses and for Intravenous Use in Beef and Dairy Cattle. Not for Use in Dry Dairy Cows and Veal Calves.

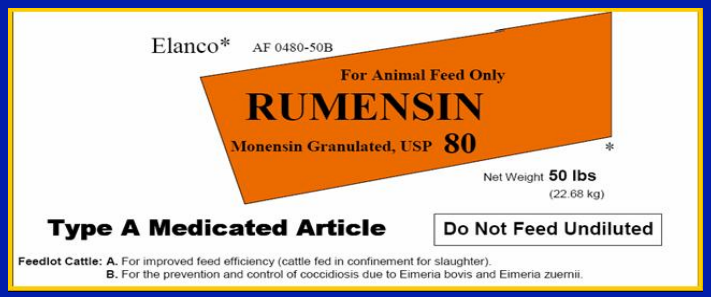
CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: Each milliliter of BANAMINE Injectable Solution contains flunixin meglumine equivalent to 50 mg flunixin, 0.1 mg edetate disodium, 2.5 mg sodium formaldehyde sulfoxylate, 4.0 mg diethanolamine, 207.2 mg propylene glycol; 5.0 mg phenol as preservative, hydrochloric acid, water for injection q.s.

PHARMACOLOGY: Flunixin meglumine is a potent, non-narcotic, nonsteroidal, analgesic agent with anti-inflammatory and antipyretic activity. It is significantly more potent than pentazocine, meperidine, and codeine as an analgesic in the rat yeast paw test.

Horse: Flunixin is four times as potent on a mg-per-mg basis as phenylbutazone as measured by the reduction in lameness and swelling in the horse. Plasma half-life in horse serum is 1.6 hours following a single dose of 1.1 mg/kg. Measurable amounts are detectable in horse plasma at 8 hours postinjection.

Cattle: Flunixin meglumine is a weak acid ($pK_a 5.82$)[1] which exhibits a high degree of



Elanco* AF 0480-50B

For Animal Feed Only

RUMENSIN

Monensin Granulated, USP **80** *

Net Weight **50 lbs** (22.68 kg)

Type A Medicated Article

Do Not Feed Undiluted

Feedlot Cattle: A. For improved feed efficiency (cattle fed in confinement for slaughter).
B. For the prevention and control of coccidiosis due to Eimeria bovis and Eimeria zuernii.

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.

New Animal Drug Application Public Documents

- Federal Register Announcement and Codification in Code of Federal Regulations
- Display of the Freedom of Information Summary and Environmental Assessment
- Submission of Final Printed Labeling

Distribution of VMPs

Article 3.4.11

- Legislation should provide for actions
  - Importing, storing, processing, wholesaling or otherwise distributing VMPs or raw materials for use in making VMPs
  - Arrangements for traceability, recall and conditions of use
  - Regulation of advertising claims and other marketing and promotional activities

Distribution of VMPs

- Conditions for transportation, storage, distribution
  - Sanitation, disinfection
  - Humidity, temperature, lighting, ventilation (controlled and recorded)
  - Inventory control (tracking system)
  - Product packaging to protect from environmental conditions
  - Expiration dates

Global Pharmacovigilance and Post Market Surveillance

- Reporting of adverse events
- With appropriate program resources, serves as early warning surveillance system
- Identify safety signals and effectiveness issues
- Identify potential drug residue or contamination issues
- Promote international collaboration, education, and training
- VICH GL 24, 29, 30, 35, 42

Our public health mission succeeds when……

……we put in the hands of the user:

- an approved,
- safe and effective,
- quality manufactured,
- properly labeled

VMPs to meet therapeutic and production needs of animals

Thank you!!!