



They're not all the same: Why FDA approval of animal drugs matters

Elizabeth Luddy, DVM
Deputy Director, Office of New Animal Drug Evaluation
Center for Veterinary Medicine
US Food and Drug Administration



How do you know the drugs you give your patients are backed up by safety and effectiveness data?



How do you know the bottle you pick up contains the actual amount of drug listed on the label?

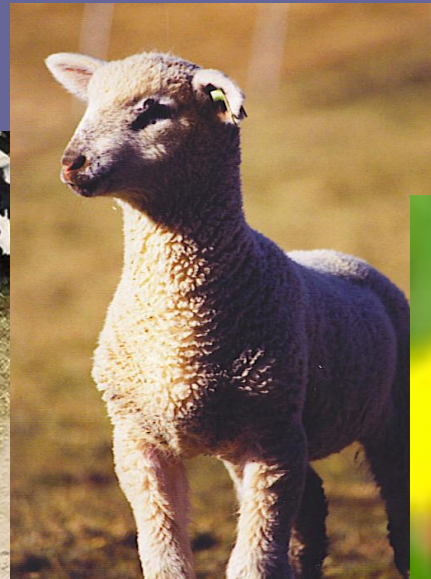
How do you know the drug is sterile?

How do you know there are no contaminants in the bottle?

How do you know if you are giving your patient a quality-made product?

Can you rely on the expiration dating and storage information?

How do you know when the edible tissues from animals treated with a drug are safe for humans to consume?



Nuflor^{GOLD}

(florfenicol) TM

Injectable Solution,
An Antimicrobial

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

NADA 141-265, Approved by FDA

NDC 0061-5327-01

 **Intervet**
Schering-Plough Animal Health

100 mL Multiple Dose Vial • 300 mg/mL • Sterile

Nuflor^{GOLD}

(florfenicol) TM

Injectable Solution, An Antimicrobial
For subcutaneous use in beef and non-lactating dairy cattle only

Not for use in female dairy cattle 20 months of age or older or in calves to be processed for veal

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

NADA 141-265, Approved by FDA

 **Intervet**
Schering-Plough Animal Health NDC 0061-5327-01

100 mL Multiple Dose Vial • 300 mg/mL • Sterile

NADA 141-123, Approved by FDA

Contains 7 Syringes
Individually Wrapped

Product 3661101



GastroGard®
(omeprazole) Oral Paste for Equine Ulcers

For Treatment and Prevention of Recurrence of Equine Gastric Ulcers

- GastroGard® (omeprazole) Paste for Equine Ulcers contains 3.3% omeprazole.
- Omeprazole is one form of active ingredient used to produce this.
- GastroGard is a well accepted, flavored paste formulation.
- GastroGard Paste is a daily oral paste for maintenance. Dispensed from a syringe.

Dosing in the Groom

- For treatment of gastric ulcers, GastroGard Paste should be administered only once a day for 4 weeks at the recommended dosage of 18 mg omeprazole with body weight (1 mg/kg).
- For the prevention of recurrence of gastric ulcers, a 6-week treatment for at least an additional 4 weeks by administering GastroGard Paste at the recommended daily maintenance dose of 18 mg/kg (1 mg/kg).

Directions for Use

- GastroGard Paste for horses is recommended for use in horses and foals 4 months of age and older.
- For the treatment of equine gastric ulcers, each syringe will dispense up to 3.30 g body weight.
- For the prevention of recurrence of equine gastric ulcers, each syringe will dispense up to 3.30 g body weight.

Warnings

- When GastroGard Paste was administered to provide omeprazole at 1.8 mg/kg/day for 4 weeks, it effectively healed or reduced the severity of gastric ulcers in horses and foals in experimental studies conducted at locations across the United States.
- Subsequent daily administration of GastroGard Paste to provide omeprazole at 1.8 mg/kg/day for 4 weeks prevented recurrence of gastric ulcers of untreated horses. Ulcers reappeared however in horses returned from GastroGard Paste treatment.

Safety

- GastroGard Paste has an adequate margin of safety in horses and foals.
- GastroGard Paste was well tolerated in control and in the study studies in at least 120 horses (including controls) across the United States.

Signs of Ulcer Disease

- The reported incidence of gastric ulcers in performance horses is high (up to 90%) (see equine adaptation) (see 010101).
- Clinical signs of gastric ulcers are loss of appetite, poor appetite and poor performance, weight loss.

Package Contents

- 7 syringes per carton.
- Each syringe contains 3.30 g of omeprazole in a well accepted, flavored paste formulation.

Storage

- Store at 60°F - 75°F (16°C - 24°C). Excursions between 59°F - 86°F (15°C - 30°C) are permitted.

Caution

- Federal (LDA) law restricts this drug to use by or on the order of a licensed veterinarian.

Warnings

- Do not use in horses intended for human consumption.
- Keep this and all drugs out of the reach of children. In case of gastric by horses, contact a physician.

Customer Assistance

- For more information, please call 1-800-833-4343.

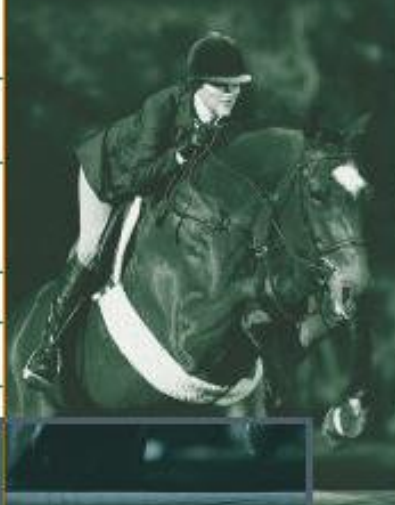
READ PACKAGE INSERT FOR FULLER INSTRUCTIONS AND IMPORTANT INFORMATION.

Merial Inc.
 Merck & Co., Inc.
 Kenilworth, NJ 07033
 GastroGard is a registered trademark of the
 Merial Group of Companies.
 ©2009 Merial. All rights reserved.
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 Rev 04 2009



3 50604-37041 3

GastroGard®
(omeprazole) Oral Paste for Equine Ulcers



Improves and Heals Gastric Ulcers

Prevents Gastric Ulcer Recurrence

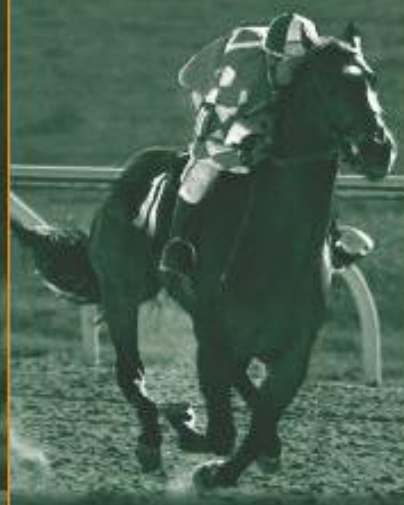
Once-a-Day Dosing

NADA 141-123, Approved by FDA

Contains 7 Syringes
Individually Wrapped



GastroGard®
(omeprazole) Oral Paste for Equine Ulcers



Improves and Heals Gastric Ulcers

Prevents Gastric Ulcer Recurrence

Once-a-Day Dosing

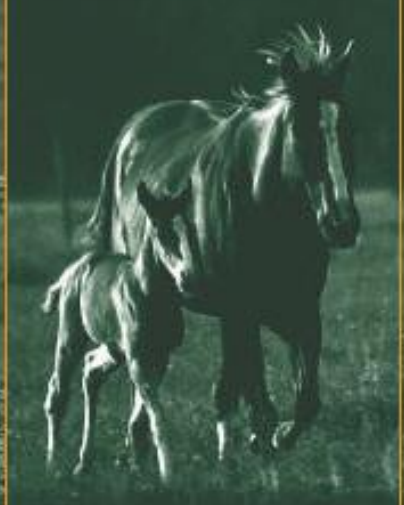
NADA 141-123, Approved by FDA

Contains 7 Syringes
Individually Wrapped

Product 3661101



GastroGard®
(omeprazole) Oral Paste for Equine Ulcers



Improves and Heals Gastric Ulcers

Prevents Gastric Ulcer Recurrence

Once-a-Day Dosing

NADA 141-123, Approved by FDA

Contains 7 Syringes
Individually Wrapped



MS 101

10110

Fig. 10a

60

30

VETORYL
(trilostane)
30 Capsules

CAUTION: Federal law restricts

NADA 141-291, Approved

NADA 141-291, Approved

CAUTION: Federal law restricts

30 Capsules
(trilostane)

VETORYL

VETORYL CAPSULES



VETORYL
(trilostane)
30 Capsules

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VETORYL

VETORYL CAPSULES



VETORYL CAPSULES
(trilostane)
30 Capsules

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

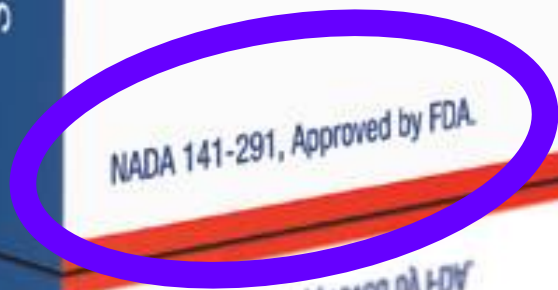
NADA 141-291, Approved by FDA

NADA 141-291, Approved by FDA

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

30 Capsules

VETORYL





2.5 mg

FELIMAZOLE™

(methimazole) Coated Tablets
100 Tablets

For oral use in cats only.

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

NADA 141-292, Approved by FDA.

See package insert for complete product information.

WARNINGS: Methimazole has anti-vitamin K activity and may induce bleeding diathesis without evidence of thrombocytopenia. See ADVERSE REACTIONS in package insert.

HUMAN WARNINGS: See package insert for complete product information.

STORAGE INFORMATION: Store at controlled room temperature 25°C (77°F) with excursions between 15°-30°C (59°-86°F) permitted. Keep the container tightly closed to protect from moisture.

DISTRIBUTED BY: Dechra Veterinary Products, 7015 College Boulevard, Suite 525, Overland Park, KS 66211.



Code No. : GO/DRUGS/536

Lot:

Mfd.:

Exp.:

DK54A

NDC 27053-001-01

SUPERIORBUTE® POWDER

(phenylbutazone)

with Sweet Apple-Flavor

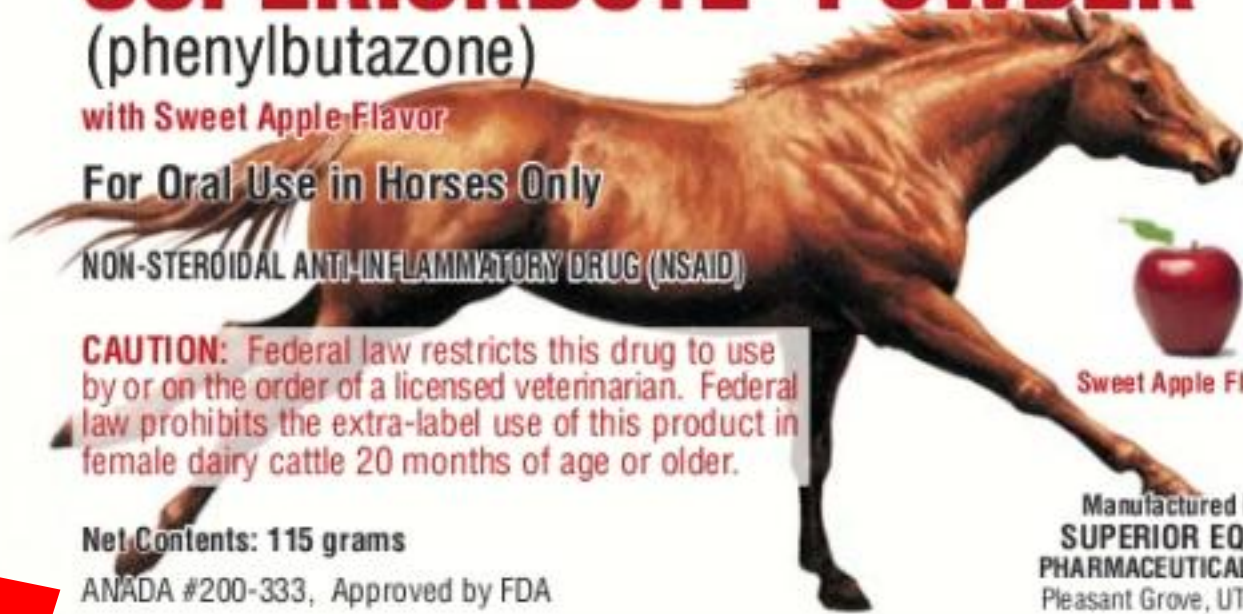
For Oral Use in Horses Only

NON-STEROIDAL ANTI-INFLAMMATORY DRUG (NSAID)

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian. Federal law prohibits the extra-label use of this product in female dairy cattle 20 months of age or older.

Net Contents: 115 grams

ANADA #200-333, Approved by FDA



Sweet Apple Flavor

Manufactured For:
**SUPERIOR EQUINE
PHARMACEUTICALS, INC.**
Pleasant Grove, UT 84062

inflammatory conditions
s. In the treatment
ns, specific

Each level scoop
lbutazone.
to 1/2 tablespoon)
dy weight, but not
ns per horse daily.
reduce to a

INSERT UNDERNEATH.

Each level s
Phenylbutaz
One level sco

RESIDU
horses

HUMAN WA
Dispense in

PRECAUTION
or corticoste

Store at room
30°C (59-86°

SUPERIORB
a registered
Equine Phar

Manufacture
VETOQUINO
Princeville, C

Made in Ca



**CA =
Conditionally
Approved by
FDA**

**"Conditionally approved by
FDA pending a full
demonstration of
effectiveness under
application number 141-308."**



PESTICIDES
(insecticides,
fungicides,
rodenticides)



ANIMAL DRUGS & DEVICES
(antimicrobials, physiologic
drugs, antiparasiticides,
production drugs)



***REGULATION OF
ANIMAL HEALTH
PRODUCTS***

VETERINARY BIOLOGICS
(vaccines, bacterins, antisera,
diagnostic kits, and other
products of biological origin)



EPA

- The Product Registration Number must appear on the label of the product preceded by the phrase EPA Registration No. or EPA Reg. No.
- The registration number may appear on any suitable location on the label or immediate container, however, it must appear on the wrapper or outside container of the package if the number cannot be clearly read through the wrapper or container.

**Foreign
Unregistered
Product**

advantage 40
For dogs less than 4 kg
For external use only
For animal
treatment only
Contains
10% w/v imidacloprid
0.4 ml
POM
Vm 0010/4100
VPA 10021/35/1
00287577
Bayer AG, Leverkusen
BN: Exp.:
WR8699 10 2000



advantage 40
Für Tiere/Hunde
Zum Auftragen auf
die Haut.
0,4 ml
Bayer
00345712
Dr-B: Verwendbar bis:
KP02AZ6 01-2006



**U.S. EPA
Registered
Product**

advantage
9.1% imidacloprid
0.4 ml
EPA Reg.
No. 11556-117
WARNING
Keep out of reach
of children
Read The Entire
Label Before Use
Bayer
00230257
LOT NO.
KPO0FSV



What's the Difference?

EPA Registered Pesticide

FDA Approved Drug

Foreign Labeled Product



advantage 55
Topical Solution

Once-a-Month Topical Flea and Lice Treatment for Dogs and Puppies 7 Weeks and Older and 21-55 lbs.

- Kills fleas on dogs within 12 hours
- Kills fleas before they lay eggs
- Convenient, easy to apply

Active Ingredient % By Weight
 Imidacloprid..... 9.1 %
 Other Ingredients..... 90.9 %
 Total..... 100.0 %
 Four 0.084 fl oz (2.5 mL) Tubes

KEEP OUT OF REACH OF CHILDREN WARNING

See back panel for First Aid.
 For Directions for Use, and Storage and Disposal, see supplemental labeling inside.



4 Pack



advantage multi
for dogs
(imidacloprid + moxidectin)
Topical Solution

CAUTION: Federal (U.S.A.) Law restricts this drug to use by or on the order of a licensed veterinarian

- Once-A-Month Topical Solution**
- Prevention of heartworm disease
 - Kills adult fleas and is indicated for the treatment of flea infestations
 - Treatment and control of hookworms, roundworms, and whipworms
 - For dogs and puppies 7 weeks of age and older and 20.1 to 55 lbs.

Do not administer product orally.
 For the first 30 minutes after application, ensure that dogs cannot lick the product from application sites on themselves or other treated dogs.
 Children should not come in contact with application sites for two (2) hours after application.

Each tube contains 250 mg of imidacloprid and 62.5 mg of moxidectin
 Keep this and all drugs out of the reach of children.

Do not use this product on cats.

NADA 8-141-231, Approved by FDA



6 Pack

SIX 2.5 mL Tubes



advocate
For Dogs 10-25 kg

100 g/L IMIDACLOPRID
 25 g/L MOXIDECTIN



advantage multi
for dogs
(imidacloprid + moxidectin)
Topical Solution

SEE PACKAGE INSERT FOR COMPLETE PRODUCT INFORMATION

POISON
 KEEP OUT OF REACH OF CHILDREN
 READ SAFETY DIRECTIONS FOR ANIMAL TREATMENT ONLY



3 x 2.5 mL

USDA Center for Veterinary Biologics (CVB)

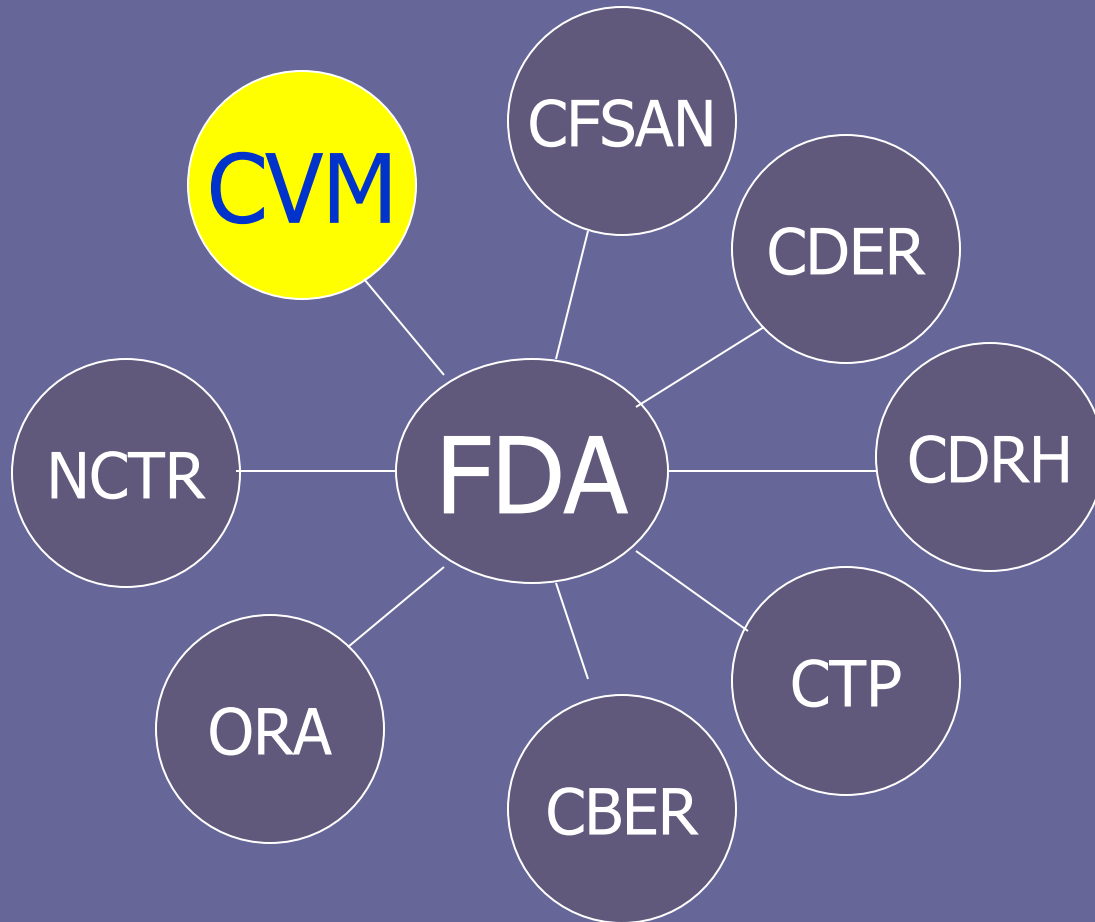
- Look for the U.S. veterinary license number on the product label when buying veterinary biologics. This assures that the product has been manufactured and tested under USDA standards.
- Under Federal law, all information on the labels of USDA-licensed biologics and in accompanying literature must be approved.
- <http://www.aphis.usda.gov/lpa/pubs/vetbiobr.pdf>

Center for Veterinary Medicine

The Center for Veterinary Medicine (CVM) regulates the manufacture and distribution of food additives and drugs that will be given to animals.



Center for Veterinary Medicine (CVM)



Center for Veterinary Medicine

Mission Statement

"Protecting Human and Animal Health"

Mission

- Protect Human and Animal Health by ensuring
 - safe and effective new animal drugs reach the market
 - unsafe and ineffective new animal drugs do not reach the market



Animal Health and Animal Food Product Safety

CVM is responsible for regulating animal drugs, devices and food additives

from:



- Animal Drug Manufacturers (300)
- Feed Manufacturers (6,600)
- Livestock and Poultry Producers (over 1 million)
- Specialized Industry/Firms

given to or used on:



- 8.5 billion chickens & turkeys
- 160 million cattle & pigs
- 11 million sheep & goats

consumed by:

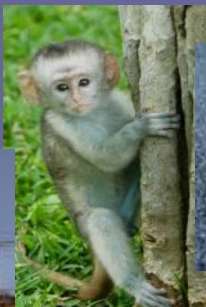


- 300 million humans in the U.S.

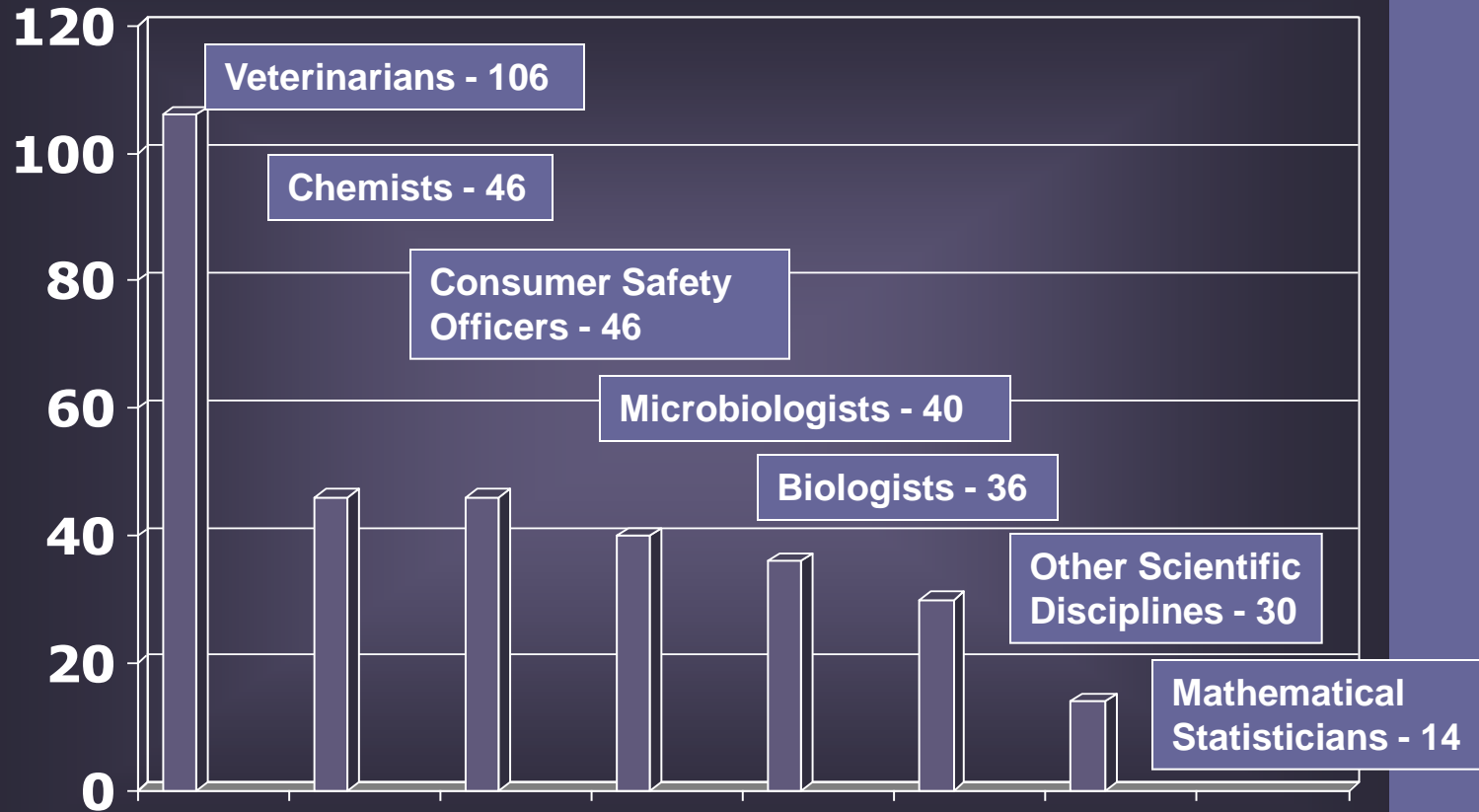
Companion Animal Medicine and Minor Species

CVM is responsible for regulating drugs, devices and food additives used in companion animals (dogs, cats and horses) and minor animal species...

- 65 million dogs & 75 million cats
- 9.5 million horses
- minor species include all animals other than cattle, swine, chickens, turkeys, horses, dogs and cats



Scientific and Technical Disciplines at CVM



Graph does not display 100% of CVM staffing

Currently 438 employees - July 2009

Office of New Animal Drug Evaluation (ONADE)

Reviews information submitted by drug sponsors who want to obtain approval to manufacture and market animal drugs



Legal Marketing of Animal Drugs

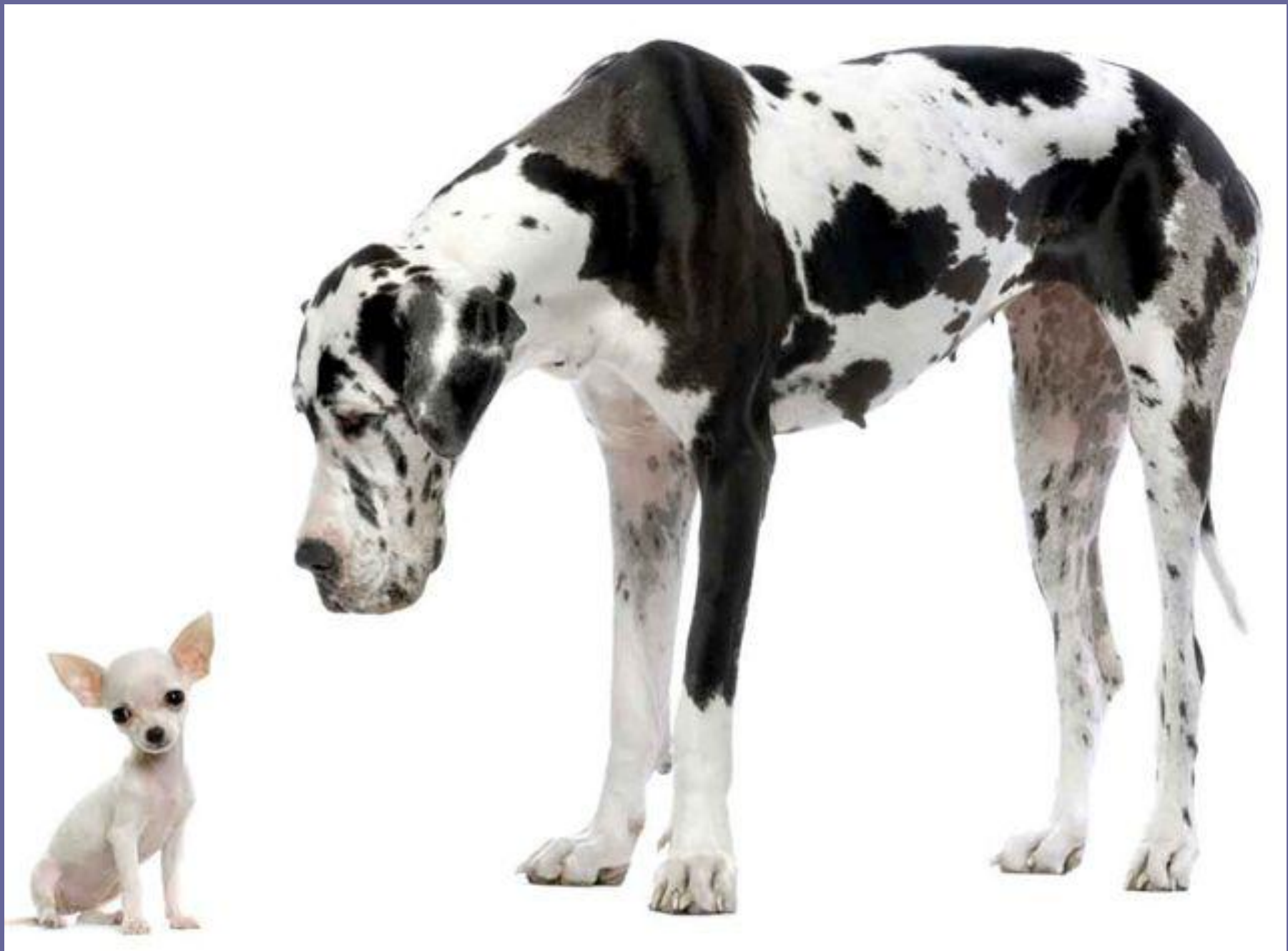
- To be legally marketed [*from section 512 of the Food, Drug, and Cosmetic Act*], an animal drug must be the subject of:
 - an approved new animal drug application (NADA)
 - an approved generic application [abbreviated new animal drug application (ANADA)]
 - a conditional approval or
 - an index listing

What does an approved new animal drug application (NADA) mean?



NADA XXX-XXX,
Approved by FDA

- 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



Technical Sections of an NADA

- **Target Animal Safety**
- **Effectiveness**
- **Chemistry, Manufacturing, and Controls**
- **Human Food Safety**
- **Environmental Impact**
- **Labeling**
- **All Other Information**

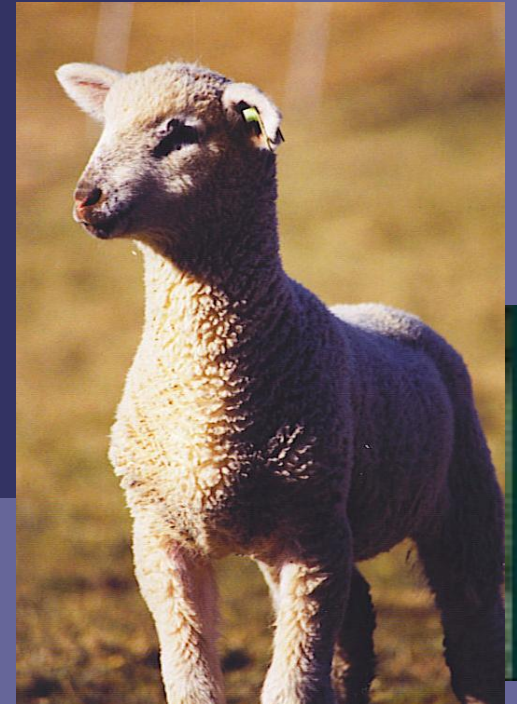


TARGET ANIMAL SAFETY
DEFINITION OF SAFETY

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

TARGET ANIMAL SAFETY

- **Margin of Safety study (0X, 1X, 3X, 5X)**
- **Reproductive Safety study**
- **Animal Class Safety study**
- **Special cases
(specific breeds, injection site
irritation)**



TARGET ANIMAL SAFETY

- Identify the toxic effects and establish a margin of safety
- Generally conducted in a small number of healthy animals
- An approval may not require all of the types of safety studies
- Safety information is also collected during the effectiveness studies

USER SAFETY



- **Potential hazards associated with:**
 - **manufacturing**
 - **direct - occupational exposure**
 - **indirect - manufacturing emissions**
 - **administration to animals**

EFFECTIVENESS

DEFINITION OF EFFECTIVENESS

Substantial evidence consisting of one or more adequate and well controlled investigations, such as

EFFECTIVENESS

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



EFFECTIVENESS

- Show that the drug is effective compared to a control (usually a placebo control or a positive control) when administered by the intended label instructions
- Field “conditions of use” studies
- Requires adequate and well-controlled studies as are necessary to show the new animal drug will have its intended effect



CHEMISTRY, MANUFACTURING, AND CONTROLS

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

- **Methods and controls**
- **Stability data**
- **Good Manufacturing Practice (GMP) compliance verification - pre-approval inspection**

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

REGULATORY METHOD:

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

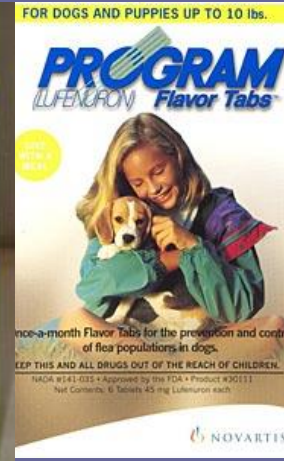
ENVIRONMENTAL IMPACT



- **Categorical Exclusion or**
- **Environmental studies**
- **Environmental assessment**

LABELING

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



Main Labeling Components

Package Insert

- Written for veterinarians

Client Information Sheet

- Written for owners
- Accompanies certain drug products



Bottle/Vial/Outer Box Labeling

Labels as “Living” Documents

Post-marketing experience, including Adverse Drug Experiences (ADEs)

Sponsor-initiated updates

- Manufacturing changes
- New tablet sizes



ALL OTHER INFORMATION

- **foreign marketing experience**
- **reports of pilot studies**
- **literature reports**



The drug can be legally marketed, promoted, and used.



Drug Development Statistics

- **The development and FDA approval of a major new animal drug takes 7-10 years**
- **The cost to develop a major new animal drug can cost up to \$100 million**

reference: Animal Health Institute (AHI)

<http://www.ahi.org/about-animal-medicines/industry-statistics/>

How do you know?

Legal Standards

FDA required testing

FDA evaluation

FDA inspections

FDA generated label

Continued monitoring after approval

Enforcement

Animal & Veterinary

Home > Animal & Veterinary

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<http://www.fda.gov/AnimalVeterinary/default.htm>

Spotlight

- 3-Nitro (Roxarsone) and Chicken
- About the Center for Veterinary Medicine (video)
- Animal Feed (video)
- Food Registry for

Unapproved Animal Drugs

FDA has serious concerns about unapproved animal drugs. These drugs are not reviewed by FDA and may not meet FDA's strict standards for safety and effectiveness.



Development & Approval Process

New Animal Drug Applications, Electronic Submissions, User Fees, Genetic Engineering, Minor Use/Minor Species, Aquaculture, Food Additive Petitions

[Guidance, Compliance & Enforcement](#)

Resources for You

Animal Health Literacy, Consumer Information, FDA and the Veterinarian

Safety & Health

Adverse Drug Events, Product Safety, Animal Food Safety System (AFSS), Antimicrobial

Alerts

- Recalls
- Pet Food Recalls
- How to Report a Pet Food Complaint
- Veterinary Adverse Event Voluntary Reporting
- Veterinary Adverse Event Reporting for Manufacturers

Approvals & Clearances

- New Animal Drug

Check to see if a drug is approved
Animal Drugs@ FDA

BSE, Policies & Procedures Manual, Laws, Salmonella and Turtle Safety

News & Events

CVM Updates, FDA Veterinarian Newsletter, Meeting Announcements

Products

Approved Animal Drug Products, Animal Food/Feed, Imports & Exports, Generally Recognized as Safe (GRAS) Notification Program

Resistance, Animal Cloning, Recalls

Science & Research

Research Areas, Publications

Applications

- [Animal Drugs @ FDA](#)

CVM Information

- [About the Center for Veterinary Medicine](#)
- [CVM Ombudsman](#)
- [Veterinary Medicine Student Internships](#)
- [CVM FOIA Electronic Reading Room](#)

Look at the data supporting approved drugs

Resources for You

- [Follow Us on Twitter](#)
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- [Veterinary Medicine Advisory Committee](#)
- [Frequently Asked Questions](#)
- [Federal Register Notices](#)

Search Animal & Veterinary

News & Events

- [Nestlé Purina Recalls Limited Number of Dry Cat Food Bags Due to a Potential Health Risk \(Shipped Only to Colorado, Idaho and Oregon\)](#)
- [FDA Announces Upcoming NARMS Meeting](#)
- [June 2011 Green Book Monthly Update \(PDF - 16KB\)](#)
- [FDA Announces Minor Use/Minor Species \(MUMS\) Grant Program Request for Applications Due by August 5](#)
- [FDA: Pfizer will voluntarily suspend sale of animal drug 3-Nitro](#)

[More News & Events](#)

Contact Us

Center for Veterinary Medicine
☎ 240-276-9300
✉ AskCVM@fda.hhs.gov
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Rockville, MD 20855

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Contact CVM by email or phone

CVM – Protecting Human and Animal Health



Thank You!

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240-276-8312

