UNAPPROVED VETERINARY DRUGS

Janice Steinschneider
Supervisory Regulatory Counsel

Office of Surveillance & Compliance
FDA/Center for Veterinary Medicine

USP Veterinary Drugs Stakeholder Forum
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December 20, 2010: FDA issued Federal Register Notice (FRN) on unapproved animal drugs

Requested comments on strategies to address the prevalence of animal drug product marketed in the United States without approval or other legal marketing status

Utilize existing statutory/regulatory framework in different ways. Notice in particular asked about:
- Monographs
- Publicly available literature
Section 512 of the FDCA: new animal drugs must have a

- New animal drug application (NADA)
- Abbreviated new animal drug application (ANADA)
- Conditional approval – for minor uses or minor species
- Index listing (Index of Legally Marketed Unapproved New Animal Drugs) – for minor, non-food species
The New Animal Drug Approval Requirement

- Use must conform to the approved label (except for legal extralabel use)
- FDCA exceptions to the approval requirement are very narrow
- Few if any currently marketed unapproved animal drugs can meet them
Many drugs for animals are marketed without an approved application/listing

Unapproved animal drugs include:

- Traditional drugs used in veterinary practice
  - Examples in the Dec. 2012 FRN: injectable vitamins, medicated shampoos, glucose solutions, antidotes, anti-infective products etc.
  - Some may be the standard of care

- Less traditional products that are drugs as defined by the FDCA: “Animal supplements”, homeopathic remedies, other complementary/alternative medicine products

- Compounded products
Adulteration, misbranding, registration & listing requirements apply to unapproved drugs

Historically, CVM has exercised “enforcement discretion” over approval requirement for some unapproved animal drugs

- Enforcement discretion refers to agency decisions to not act against a violation to e.g. preserve resources or for policy reasons

- Does not make the product legal
A relatively limited number of approved animal drugs have been available to meet the health needs of a diverse number of animal species.

CVM sometimes issued “no objection” letters or guidance documents regarding a product or class of products with no known safety issues.

Unapproved animal drugs initiative represents a shift away from enforcement discretion.
Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA): Permits extra-label use of approved animal and human drugs under the supervision of a veterinarian

Animal Drug Availability Act of 1996 (ADAA): Increased flexibility in animal drug approval process e.g. broadened types of studies that can demonstrate effectiveness; streamlined approval process for combination drugs
Minor Use and Minor Species Animal Health Act of 2004 (MUMS Act): provided for -- conditional approval of drugs for minor uses or for minor species, indexing of drugs for minor non-food species, and grants and extended periods of exclusive marketing.

Animal Drug User Fee Act of 2003: waivers from fees in some circumstances for e.g. MUMS drugs, small businesses, when fees exceed costs.
Approval process protects animals & humans from unsafe, ineffective, substandard products

Pre-market review of application
- Evidence of safety and efficacy
  - Law requires scientific evidence
  - Safety: includes human as well as animal safety

Review of Chemistry, Manufacturing and Controls (CMC): manufacturing methods will consistently produce a product with appropriate quality and stated identity, strength, and purity

Review of prescriber and patient labeling: accurate, not misleading, and complete
IMPORTANCE OF THE APPROVAL PROCESS

- Post Approval Monitoring
  - Adverse event and other post-approval reporting – continuous monitoring as drug is used in broader populations aids in identification of previously unknown safety risks or effectiveness issues

- Review of labeling and manufacturing changes

- Advertising – monitoring of advertising of approved Rx animal drugs helps ensure they are not false or misleading and present fair balance of risk and benefit information
CVM’s Current Regulatory Approach

- CVM no longer issues enforcement discretion letters except in rare circumstances
- Standard-of-care unapproved drugs will not suddenly become unavailable
- CVM is taking steps to increase availability of approved animal drugs and decrease reliance on unapproved animal drugs
CVM’S CURRENT REGULATORY APPROACH

- Working with sponsors to bring marketed unapproved drugs into approval process

- CVM understands the importance of addressing unfair competition from marketers of unapproved products when a firm obtains approval

- When firms get an approval for a marketed unapproved drug, CVM may take action to address marketed unapproved drugs that compete with the approved product
Phenylpropanolamine (PPA)

- History of use in veterinary medicine: to control urinary incontinence in dogs

- August 4, 2011: Approval of animal drug containing PPA – Proin, sponsored by Pegasus Labs

Pergolide

- History of veterinary use: to treat Equine Cushing’s Disease

- September 7, 2011: Approval of animal drug containing pergolide – Prascend sponsored by Boehringer Ingelheim Vetmedica
CVM response to approval of PPA and Pergolide animal drugs

- Issued letters to pharmacists and veterinarians
  - Notifying them of the approvals
  - Reminding them of the benefits of using approved drugs rather than unapproved drugs
  - Reminding them that animal drugs products should not be compounded from bulk PPA or Pergolide
PPA, Pergolide added to import alert 69-09 so that bulk active ingredient can go only to manufacture of approved PPA, Pergolide products

CVM expects that more marketed unapproved animal drugs will obtain approvals

CVM aware of CDER unapproved drugs warning letters and Federal Register Notices and may take similar enforcement action as appropriate

CVM encourages firms marketing approved products to provide information about unapproved competitors
Potassium Bromide (KBR)
- History of use to treat seizures in dogs

CVM staff reviewed published literature
- Results published in JAVMA, Vol 240, No. 6, March 15, 2012

“A Systematic Review of the Safety of Potassium Bromide in Dogs,” Hope E. Baird-Heinz, dvm; A’ndrea L. Van Schoick, dvm; Francis R. Pelsor, pharmd; D. Lauren Raniv and, mph; Laura L. Hungerford, dvm, mph, phd

www.fda.gov/downloads/AnimalVeterinary/ResourcesforYou/u/UCM308426.pdf
Review is available for use in applications for KBr drugs for dogs

An example of literature review that might be done to support applications for other unapproved animal drug with long history of use and many literature