UNAPPROVED VETERINARY DRUGS

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INITIATIVE TO ADDRESS UNAPPROVED ANIMAL DRUGS

- 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

THE NEW ANIMAL DRUG APPROVAL REQUIREMENT

- 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

MARKETING OF UNAPPROVED ANIMAL DRUGS

- 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

MARKETING OF UNAPPROVED ANIMAL DRUGS

- 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

MARKETING OF UNAPPROVED ANIMAL DRUGS

- 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

FDCA AMENDMENTS INCREASE AVAILABILITY OF APPROVED DRUGS FOR VETERINARY USE

- 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

FDCA AMENDMENTS INCREASE AVAILABILITY OF APPROVED DRUGS FOR VETERINARY USE

- 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.

IMPORTANCE OF THE APPROVAL PROCESS

- 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

APPROVAL OF ANIMAL DRUGS PREVIOUSLY MARKETED WITHOUT APPROVAL

- 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 Pegaus 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

APPROVAL OF ANIMAL DRUGS PREVIOUSLY MARKETED WITHOUT APPROVAL

- 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

APPROVAL OF ANIMAL DRUGS PREVIOUSLY MARKETED WITHOUT APPROVAL

- 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

USE OF EXISTING PUBLISHED LITERATURE

- 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/UCM308426.pdf

USE OF EXISTING PUBLISHED LITERATURE

- 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