Veterinary Food and Drugs

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Outline

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- Animal Drugs
- Postapproval Responsibilities
- Veterinary Biological Drugs

Resources

- Animal Drugs: Future Stepchild or Pioneer, 55 Food & Drug LJ 33

Overview

- FDA – Federal Food, Drug, and Cosmetic Act (FDCA)
  - ✓ Nonbiological animal drugs and animal foods regulated by FDA
  - ✓ Definitions of “foods” and “drugs” include use “for man or other animals,” sections 201(f), (g), respectively
  - ✓ Subject to various controls in Chapters IV and V FDCA
  - ✓ Major categories:
    - Used in nonfood-producing animals
    - Used in food-producing animals
- USDA – Virus-Serum-Toxin Act
  - ✓ Biological drugs (drugs generally characterized by their interaction with animal immune system) regulated by USDA to ensure biologicals are safe, pure, and potent

Animal Food – AAFCO

- American Feed Control Officials (AAFCO), Model Commercial Feed Law – State and Industry regulation of pet foods, nonmedicated livestock feed, and medicated feeds with drug levels < FDA licensing requirements
  - ✓ Livestock feed – registration, composition, sale, labeling rules, ingredients as GRAS
    - AAFCO feed ingredient definition approval process
    - FDA/CVM accepts animal feed GRAS notifications as alternative to AAFCO feed ingredient definition approval process
  - ✓ Livestock feed and pet food – labeling, compositional information (guarantees)
  - ✓ Pet food – nutritional use of food and substantiation of claims

Animal Food – FDA

- Medicated feeds within FDA licensing concentrations, Section 512(m) FDCA
  - ✓ Registration and licensing, inspection
- Pet food safety, Food and Drug Administration Amendments Act (FDAAA) 2007
  - ✓ Provisions for regulations on ingredient standards and definitions, processing standards, updated standards for labeling (including nutritional and ingredient information)
  - ✓ Early warning and surveillance system
  - ✓ Pet food recalls and mandatory reporting
  - ✓ Reportable Food Registry - mandatory reporting where there is reasonable probability that use of, or exposure to, an article of food will cause serious adverse health consequences or death to humans or animals
- Livestock Feed (including pet food), Food Safety Modernization Act (FSMA) 2011
  - ✓ Manufacturers required to conduct hazard evaluation, and identify and implement preventive controls (including GMPs), sanitary transportation, intentional adulteration, foreign supplier verification
  - ✓ Mandatory recall – reasonable probability that use of or exposure to food will cause adverse health consequences or death to humans or animals
- Medicated Feed – regulated as a food and drug
  - ✓ Animal Drug Availability Act (ADAA) 1996 – licensing feed mills on basis of GMP compliance
    - "Second Generation Program" – Type A Medicated Articles with no withdrawal period without need for medicated feed application or comply with other requirements (registration and inspection)

Animal Drugs

- "New Animal Drug" – "any drug intended for use for animals other than man, including any drug intended for use in animal feed," section 201(v) FDCA. See also 21 CFR Parts 510 – 514.
  - ✓ New animal drug considered to be adulterated unless FDA has approved a New Animal Drug Application (NADA), an Abbreviated New Animal Drug Application (ANADA), or conditional approval or indexing of drugs for minor uses or minor species, sections 512(a) and 501(a) FDCA
- Overview New Animal Drug Approval Process
  - ✓ Research & Develop Phase – pilot or bench studies
  - ✓ Pre-INADA Meeting (Pre-Investigational New Animal Drug Application Meeting)
  - ✓ Preclinical
    - Preclinical exemption for "research animals" at 21 CFR Part 58 limited to studies that are not conducted in target species
    - Institutional Animal Care and Use Committees (IACUCs) oversee ethical and humane care and use of study animals
  - ✓ Investigational New Animal Drug file (INAD) – allows manufacturer to ship unapproved investigational drug products in interstate commerce to conduct research to collect safety and efficacy data
    - Clinical studies conducted in accordance with GCPs

Animal Drugs

- New Animal Drug Approval Application (NADA) Overview
  - ✓ Technical Sections
    - Chemistry, Manufacturing, and Controls (CMC): Product Characterization Statement and description manufacturing process and controls
    - Human Food Safety: food products made from treated animals are safe for human consumption
    - Target Animal Safety
    - Effectiveness
    - Environmental Impact: how environment will be affected by approval of proposed new drug product
    - All Other Information
    - Labeling
    - Freedom of Information (FOI) Summary
  - ✓ Approval – by specific regulation that details active ingredient, product's specifications, sponsor, and conditions, indications, and limitations of use

Animal Drugs

- New Animal Drug Approval Application (NADA) Overview, Technical Sections (cont'd)
  - ✓Chemistry, Manufacturing, and Controls (CMC) Technical Section, section 512 FDCA
    - General Information
    - Manufacture
    - Characterization
    - Control of Drug Substance
    - Reference Standards
    - Container Closure System
    - Stability

Animal Drugs

- NADA Overview, Technical Sections (cont'd)
  - ✓ Human Food Safety– purpose of human food safety regulations is to ensure that food is safe for human consumption regardless of the use of an animal drug in a food-producing animal
    - Goals: identify no-observable adverse effect level (NOAEL), establish acceptable daily intake (ADI) for humans consuming drug residues, and label requirements
    - Analysis of Drug Residues – demonstrate "reasonable certainty of no harm," 21 CFR Part 514
      - Sponsor has burden od showing new animal drug is safe for use and conduct studies to demonstrate that "edible tissues from treated animals can be consumed daily in the human diet for a lifetime with no adverse effect."
      - Analysis of residues
      - Toxicology
      - Residue Chemistry
      - Microbial Food Safety
      - Regulatory Method Relied Upon by Sponsor
    - Regulating New Animal Drugs with Cancer-Causing Potential
      - Delaney Clause, section 512(d)(1)(I) FDCA – FDA is prohibited from using compounds found to induce can cancer in humans or animal
      - DES Proviso – cancer-causing drug may be approved if "Sensitivity-of-Method procedures are conducted and regulatory methods establish that "no residue of that compound will be found in the food produced from those animals under conditions of use reasonably certain to be follows in practice."

Animal Drugs

- NADA Overview, Technical Sections (cont'd)
  - ✓ Target Animal Safety
    - "safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling," section 512(d)(2) FDCA:
      - Whether and how probable it is that drug will be later consumed in or on food
      - Cumulative effect, considering all chemically-related compounds, of drug on man or animals
      - Margin of safe use of drug
      - Whether conditions of use in product labeling are likely to be followed
    - Postapproval Reporting Obligations, 21 CFR Part 514
      - 3-Day Field Alerts – product and manufacturing defects resulting in serious adverse drug events
      - 15-Day NADA/ANADA Alert Reports – serious, unexpected adverse drug events
      - Periodic Reports – filed every 6 months for first 2 years and annually
      - New animal drugs contained in animal feed, 21 CFR 510.301

Animal Drugs

- New Animal Drug Approval Application (NADA) Overview, Technical Sections (cont'd)
  - ✓ Effectiveness Technical Section
    - Dosage characterization
    - Substantial evidence (e.g., dose confirmation and clinical field studies)
    - All other information related to effectiveness
    - Proposed effectiveness-related labeling, and
    - Effectiveness section of FOI summary of safety and effectiveness studies
  - ✓ Effectiveness – "substantial evidence" that drug will have effect it is purported or represented to have under conditions of use contained in product labeling, section 512(d)(3):
    - Studies in target species
    - Laboratory animal studies
    - Field studies
    - Bioequivalence study, or
    - In vitro study

Animal Drugs

- New Animal Drug Approval Application (NADA) Overview, Technical Sections (cont'd)
  - ✓ Environmental Impact Section
    - National Environmental Policy Act (NEPA) – requires federal agencies to evaluate "Major Actions" as to whether they pose a significant impact on environment
    - Categorical Exclusions, 21 CFR 25.5 – actions that do not have significant impact on human environment
    - Environmental Assessments (EAs), 21 CFR 25.40
      - Finding of No Significant Impact Statement (FONSI Statement) – prepared by FDA when no significant environmental impact is expected
      - Environmental Impact Statement (EIS) – must be included in application if EA) suggests significant risk for environmental impact
    - Environmental Impact Statements (EIS), 21 CFR 25.42 – discussion of potential environmental impacts that cannot be avoided if proposed action implemented

Animal Drugs – Types of NADAs

- Therapeutic NADAs Intended for Non-Food Animals – new animal drugs intended to treat diseases in animals not traditionally consumed as food
- Therapeutic Drug NADA in Food Animals
  - ✓ Food use authorization – withdrawal period: requirement that drug not be administered to animal for specified period of time before its introduction into food supply
  - ✓ Human Food Safety technical section must include data on toxicology, drug residue chemistry
  - ✓ Sponsor must propose tolerance level for safe human exposure to drug residues and/or appropriate withdrawal period
- Animal Drug NADA with Non-Therapeutic Indications
  - ✓ "structure-function" – production/efficiency claims
  - ✓ NADA-related studies generally larger to determine whether claim effect is supported by appropriate data and risk-benefit supports continued availability
- Medicated Animal Feed (Type A Medicated Article) – feeds that are diluted into animal feed
  - ✓ Sponsors must submit information detailing specific analytical method used to determine amount of drug product in given amount of animal feed; once approved, FDA makes analytical methods publicly available
  - ✓ FDA generally leaves regulation of animal feed mills to states
  - ✓ cGMPs at 21 CFR Parts 225 and 226

Other Types New Animal Drug Applications

- Generic Animal Drugs
  - ✓ Generic Animal Drug and Patent Term Restoration Act 1988: generic animal drugs must meet all regulatory requirements for new animal drugs, same postmarketing requirements, and manufactured to same standards as reference drug
    - Generic Investigational New Animal Drug (GINAD)
    - Abbreviated New Animal Drug Application (ANADA): does not need to include safety information, but must meet all CMC requirements and demonstrate that drug is bioequivalent to reference drug
- Minor Use and Minor Species – granted 7 years market exclusivity
  - ✓ Minor Use and Minor Species Animal Health Act 2004 (MUMS Act): intended to make more medications available to veterinarians and animal owners to treat minor animal species and uncommon diseases in major animal species
  - ✓ Conditional approval – available once product has met safety and standards of approval, but has only demonstrated "reasonable expectation" of effectiveness
  - ✓ Conditionally approved MUMS drugs required to complete and submit required effectiveness data
  - ✓ Sponsors must renew conditional approvals each year, up to five years
  - ✓ Indexing – MUMS drugs for minor species or too rare diseases
- Genetically Engineered Animals
  - ✓ FDA asserts jurisdiction over entire animal itself as it "contains a new animal drug," *Int'l Ctr. For Tech. Assessment, et al. V. Thompson, et al.*, 421 F.Supp.2d 1 (D.D.C. 2006)
  - ✓ Review process dramatically different than "conventional" new animal drugs

Postapproval Responsibilities

- Changes to approved application
  - ✓ Manufacturing Changes – risk-based system
    - Prior Approval Supplement: highest risk changes
    - Changes Being Effected in 30 Days (CBE-30) Supplement: Lower risk changes
    - Changes Being Effected (CBE-0) Supplement: even lower risk changes
    - Minor Changes and Stability Report (Annual Report): lowest risk changes
- Withdrawal
  - ✓ Circumstances that include sponsor fraud, FDA finding that new information shows that drug is unsafe or ineffective under approved conditions for use
  - ✓ FDA must provide sponsor with notice and opportunity for formal hearing

Veterinary Biological Drugs

- USDA – Virus-Serum-Toxin Act
  - ✓ Biological drugs (drugs generally characterized by their interaction with animal immune system) regulated by USDA, Animal and Plant Health Inspection Service – safe, pure, and potent
  - ✓ Requirements include experimental permits, licensing requirements, product standards, and standardized test procedures, 9 CFR 102.3, 103.1, Part 113
  - ✓ Monitors biologics manufacturing through batch certification, 9 CFR 113.3
  - ✓ Enforcement tools of Federal Meat Inspection Act, including product detention, seizure, injunction