COMPOUNDING REGULATORY PERSPECTIVE

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COMPOUNDED ANIMAL DRUGS AS UNAPPROVED ANIMAL DRUGS

- Compounding of animal drugs by pharmacies raises same concerns as other unapproved animal drugs
- No premarket review to demonstrate the drug is safe, effective, properly labeled, and made according to processes that produce a product of expected identity, strength, purity, etc.
- If compounded drug is for a food animal, there may be little or no data on which to base a withdrawal time, and unsafe tissue residues may occur

COMPOUNDED ANIMAL DRUGS AS UNAPPROVED ANIMAL DRUGS

- No mandatory reporting to the FDA of adverse events, drug experiences
- Minimal FDA oversight over advertising claims
- Compounded drugs may unfairly compete with approved products
- Manufacturing methods in pharmacies do not meet regulatory GMPs under Part 211

COMPOUNDED ANIMAL DRUGS AS UNAPPROVED ANIMAL DRUGS

- CVM acknowledges that animal drug compounding has been a part of veterinary practice to address the need for products to treat many conditions in many different species, some with unique physiological characteristics.

- As described below, CVM animal drug compounding enforcement policies aim to limit animal drug compounding to circumstances in which the benefits to an animal's health outweigh the risks of unapproved products to public and animal health and the integrity of the approval process

LEGAL STATUS OF ANIMAL DRUG COMPOUNDING

- Food, Drug, and Cosmetic Act (FDCA): FDCA does not
  - Generally distinguish drugs made by pharmacies/practitioners from drugs made by pharmaceutical firms
  - Generally define manufacturing or compounding
  - Generally exempt drugs made by pharmacies from adulteration or misbranding provisions
  - Exempt drugs made by pharmacies from animal drug approval requirements in Section 512

LEGAL STATUS OF ANIMAL DRUG COMPOUNDING

- FDCA has limited exemptions from registration/listing and some inspection for drugs compounded by pharmacies that operate within local laws
- Because compounded animal drugs do not have an approved applications/index listings, compounding of animal drugs results in an unapproved new animals drug and therefore violates the FDCA
  - Any compounding from bulk substances (API) violates the FDCA
  - Compounding from finished products violates the FDCA except when requirements for extralabel use are met

COMPOUNDED DRUGS FOR HUMANS FDAMA AND SECTION 503A

- In 1997 FDAMA added Section 503A which exempts drugs made by pharmacies from the human drug approval requirement and statutory GMP requirement IF they meet 503A conditions
- 503A only applies to human drugs
- 503A has been the subject of litigation in several circuits, with conflicting results and regulatory uncertainty
- FDA's enforcement policies and priorities in regard to human drugs are found in CDER's Compliance Policy Guide (CPG) entitled "Pharmacy Compounding" (Sec. 460.200)

ANIMAL MEDICINAL DRUG USE CLARIFICATION ACT OF 1994 (AMDUCA)

- Permits extralabel use of approved animal or human drugs on the order of licensed veterinarian in the context of a valid veterinarian-client-patent-relationship
- CVM interprets compounding from finished approved drugs to be an extralabel use
- Regulations in Part 530 of the CFR that implement AMDUCA contain a specific section on compounding with finished approved products, 21 CFR 530.13. Requirements include:
  - No approved drug in the available dosage form and concentration can appropriately treat the condition diagnosed.

ANIMAL MEDICINAL DRUG USE CLARIFICATION ACT OF 1994 (AMDUCA)

(Part 530 requirements cont.)

- For food animal must compound from an approved animal drug if it can be used rather than an approved human drug
- Compounding must be done by a licensed pharmacist or veterinarian
- The compounder must follow adequate procedures and processes to ensure safety and effectiveness
- Scale of the compounding operation must be commensurate with the established need for compounded products

ANIMAL MEDICINAL DRUG USE CLARIFICATION ACT OF 1994 (AMDUCA)

(Part 530 requirements cont.)

- The compounder must follow state laws relating to the compounding of drugs for use in animals
- The compounding meets the more general requirements of Part 530. For instance:
  - Must be on the order of a licensed veterinarian with VCPR
  - Limited to situations in which the health of animal is threatened or suffering or death may result
  - Prescribing veterinarian must keep appropriate records and have labeling adequate for safe & effective use of the drug
  - For food animals, the veterinarian must establish appropriate withdrawal times and unsafe residues must not result

UNITED STATES V. FRANCK'S PHARMACY

- Franck's Pharmacy: Florida-based compounding pharmacy
- In 2009 it compounded a medication with excess selenium resulting in death of 21 polo ponies
- FDA inspected Franck's and ultimately filed suit in 2010 Florida District Court seeking an injunction to stop Franck's Pharmacy and its owener from violating the FDCA by compounding with bulk drug substances (i.e. APIs)

UNITED STATES V. FRANCK'S PHARMACY

- The district court denied the request for an injunction holding that:

  "in enacting the FDCA in 1938, Congress did not intend to give the FDA per se authority to enjoin the long-standing, widespread, state-regulated practice of pharmacists filling a veterinarian's prescription for a non food-producing animal by compounding from bulk substances"

- Appealed by FDA to the 11th Circuit Court of Appeals

- Briefs were filed but then Franck's was bought by another pharmacy

- Case moot and decision in Franck's is vacated

CVM ENFORCEMENT POLICY

- CVM animal Compounding CPG issued in 2003: provides guidance on CVM approach to violative animal drug compounding
  - "Compounding of Drugs for Use in Animals", CPG Sec. 608.400 www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074656.htm
- Defer to states on day-to-day oversight of compounding pharmacies and coordinate investigations and actions
- Concerned with pharmacies that overstep bounds of traditional practice and engage in activities that circumvent the drug approval process and provide for mass marketing of products
- Has a not all-inclusive list of factors that increase likelihood of enforcement action against a compounding pharmacy making animal drugs

CVM ENFORCEMENT POLICY

- The factors reflect these overall concerns:
  - Safety risk to animals or humans or results. Agency is also concerned about substandard products
  - Unfair competition with approved products or otherwise undermining the approval process
  - Compounding that is not driven by a veterinarian's identification of a particular need in a particular patient that must be met by a compounded product

FACTORS FAVORING ENFORCEMENT

- Non-critical situations: Compounding of drugs for use in situations (a) where the health of the animal is not threatened; and (b) where suffering or death of the animal is not likely to result from failure to treat.

- No prescription in-hand: Compounding of drugs in anticipation of receiving prescriptions, except in very limited quantities in relation to the amounts of drugs compounded after receiving prescriptions issued within the confines of a valid VCPR.

- Extralabel use prohibited drugs: Compounding of drugs that are prohibited for extralabel use in food-producing or nonfood-producing animals, under 21 CFR 530.41(a) and (b) respectively, because the drugs present a risk to the public health.

FACTORS FAVORING ENFORCEMENT

- Bulk and unapproved finished drugs: Compounding finished drugs from human or animal drugs that are not the subject of an approved application, or from bulk drug substances, other than those specifically addressed for regulatory discretion by the FDA, Center for Veterinary Medicine, e.g., antidotes (see Appendix A). Inquiries about compounding from unapproved drugs or bulk drug substances should be directed to CVM, Division of Compliance, 301-827-1168

- Human drugs with restricted distribution system (REMS) : Compounding from approved human drugs for which FDA has implemented a restricted distribution system.

- Commercial scale: Using commercial scale manufacturing equipment for compounding drug products.

FACTORS FAVORING ENFORCEMENT

- Compounding for resale: Compounding drugs for third parties who resell to individual patients, or offering compounded drug products at wholesale to other state licensed persons or commercial entities for resale.
- Non-compliance with state law: Failing to operate in conformance with applicable state law regulating the practice of pharmacy.
- Approved products available: Compounding of drugs for use in animals where an approved new animal drug or approved new human drug used as labeled or in conformity with 21 CFR Part 530 will, in the available dosage form and concentration, appropriately treat the condition diagnosed.

FACTORS FAVORING ENFORCEMENT

- Food-producing animals and human drugs: Compounding from a human drug for use in food-producing animals if an approved animal drug can be used for the compounding.
- Residues of drugs in animal-based food products: Instances where illegal residues occur in meat, milk, eggs, honey, aquaculture, or other food-producing animal products, and such residues were caused by the use of a compounded drug.
- Inadequate labeling: Labeling of compounded drugs without sufficient information, such as withdrawal times for drugs for food-producing animals or other categories of information that are described in 21 CFR 530.12.
- Withdrawal times established by pharmacist: Labeling a compounded drug with a withdrawal time established by the pharmacist instead of the prescribing veterinarian.