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Regulation of Contraceptives

VETERINARY DRUG DEVELOPMENT:
REGULATION OF STERILANTS AND CONTRACEPTIVES

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Veterinary Drug Development

- Outline of presentation
  - History of US Drug Regulation
  - Other US Agencies
  - US Submission Technical Sections
  - Comparison of the US and the EU
  - Chemistry, Manufacturing, and Controls
  - Target Animal Safety
  - Target Animal Efficacy
  - Environmental Safety
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History of Drug Regulation in the USA

- The Pure Food and Drug Act of 1906
  - Product sold can not be labeled in a false or misleading way
  - No more "secret ingredients"
  - Seminal challenge in courts
    - *United States v. Johnson* (221 U.S.488, 1911)
      - Opinion by Oliver Wendell Holmes
      - Act addressed ingredients only under "false and misleading" section
      - Efficacy is a matter of opinion in the medical community
      - …"but a very different and unlikely step to make them answerable to mistaken praise."
      - Something that is, "…false only in its commendatory and prophetic aspect…is not within the act."
      - Even the dissent opined that only clearly false claims - which were accepted as false - would fall under the act.
  - Seems the test established limited Congressional intent

History of Drug Regulation in the USA

- The Food, Drug, and Cosmetic act of 1938
  - The FD&C Act; The Act
  - The core law under which FDA regulates
  - Provides the authority for FDA to require safety data prior to marketing
    - Elixir of sulfanilamide (107 deaths)
  - Defines Congressional clear and unambiguous intent for the regulation of drugs to protect the public interests

History of Drug Regulation in the USA

- 1962 Kefauver-Harris Drug Amendments
  - Passed Congress in response to the thalidomide experience
  - Drug efficacy added as a requirement and greater drug safety standards permitted
- 1968 Animal Drug Amendments
  - Set all animal drug provisions in one spot for efficiency of regulation

- Sets standards for Labeling, Safety, Efficacy and Quality for New Animal Drugs in the US

Other Regulatory Agencies In the US

- **Animal and Plant Health Inspection Service (APHIS), and the Center for Veterinary Biologics (CVB) of the USDA**
  - Virus Serum Toxin Act of 1913
  - Section 902(c) of the FD&C Act states: "Nothing contained in the Act shall be construed as in any way effecting, modifying, repealing, or superseding the provisions of…the virus, serum, toxin, and analogous products provisions of 37 Stat 832-833
  - FDA view, animal biologicals are drugs, but are regulated by VST Act and, therefore, USDA
  - Memorandum of Understanding to define jurisdiction on some products
  - Disease basis of regulation

Other Regulatory Agencies In the US

- **Environmental Protection Agency (EPA)**
  - Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) of 1947
  - Toxic Substances Control Act (TOSCA) of 1976
  - Basis for regulation of crop protection chemicals
  - Basis for related products to treat pests on animals
  - Products carried dual registration late into the 1970s
  - Memorandum of Understanding between EPA and FDA set up current criteria for defining jurisdiction (mode of action and classification of target)

US Submission Technical Sections

- Initial Thoughts on the Compound
  - What will the molecule do?
    - Class
    - Structure
    - Route of administration
    - Species
  - Can the molecule be used safely?
    - Target Species
    - Those in contact with the molecule
  - The initial draft label.
    - Foremost a labeling law
    - Guides the process
  - The program of development.
    - Outlines the studies needed to gain approval

US Submission Technical Sections

- The New Animal Drug Application
  - Guidance for Industry #132 Administrative Applications and the Phased Review Process
  - Technical Section Definitions
    - Chemistry, Manufacturing, and Controls
    - Effectiveness
    - Target Animal Safety
    - Human Food Safety
    - Environmental Impact
    - Labeling
    - All Other Information

Comparison of the US and the EU

EU PART	PART I	PART II	PART III	PART IV
US Official terms	Administrative Components	Chemistry, Manuf. & Controls	Human Food Safety	Safety and Effectiveness
(Detailed terms)		CMC Technical Section (514.1)	Human Food Safety Technical Section (514.1)	Target Animal Safety Technical Section (514.1)
			Environmental Technical Section (514.1)	Target Animal Effectiveness Technical Section (514.1)
				All Other Information Technical Section (514.1)
Detailed Sections	IA Cover letter Form FDA 356V (21 CFR 514.1)	IIA Components and Compostion	III A Safety Documentation	IV I Lab Animal Safety
		IIB Manufacture	A 1 Acute toxicity	IV IA Pharmacokinetics
		IIC Methods	A 2 Subacute toxicity	IV IB Complete TAS Study
	IB Labeling Tech Section FOI Tech Section	IID Facilities and	A 3 Chronic toxicity	IV C Guidance 152
		IIE Controls	A 4	
		IIF	A 5	
		IIG	A 6 Environmental Safety	
		IIQ		
	IC DACS: none required		III B Methods of Residues	IV II Substantial Evidence of Efficacy
			B 1	
			B 2	
			B 3	

Comparison of the US and the EU

Technical Section		EU Dossier Section
Chemistry, Manufacturing, & Controls Components and Composition Methods, Facilities, and Controls		Part II Part II, Section IIA Part II, Section IIC,D,E,F,G
Effectiveness Dose Justification Clinical Field Studies "Substantial Evidence of Effectiveness"		Part IV, Section II
Target Animal Safety Laboratory animal safety data PK data Discussion of dose justification Complete multiple dose study Evidence of resistance, if applicable		Part IV, Section I Section IA3 Section II Section IB Section IA2
Human Food Safety (if applicable) Metabolism studies Toxicology studies Residue method(s) Residue depletion studies Safe concentration and withdrawal time		Part III, Section A2 Section A3 Section B3 Section B2 Part III Conclusions
Environmental Safety EA or request for exclusion		Part III, Section A6
Labeling		Part I, Section IB
Freedom of Information Summary Extracted from other Technical Sections		Part I, Section IB (Most similar to the SPC)
All Other Information Published literature Internal data, including mkt. experience in other countries		May find in Parts III and IV

Comparison of the US and the EU

- European Approach
  - European Medicine Agency
  - Committee for Veterinary Medicinal Products
  - All EU Member States apply same standards
  - Approval Processes differ
    - National
    - Mutual Recognition
    - Decentralized
    - Central
  - Data requirements very similar
  - Often see global programs of development
  - Safety, Efficacy, Quality again the standards

Data Requirements

- Chemistry, Manufacturing, and Controls
  - 21 CFR 514.1 (b) (4), (5), (6)
  - Components and Composition
  - Manufacturing methods, facilities, and controls

Data Requirements

- Chemistry, Manufacturing, and Controls
  - Components and Compositions
    - “A complete list of all articles used in for production of the new animal drug including a full list of the composition of each article”
    - “Components” include materials used in the synthesis, extraction or other method of preparation of the active ingredient and of the drug product, with reasonable alternatives
    - “Composition” includes the name and amount of each ingredient, active and excipient; a representative batch formula, with all components whether they are in the final product or not

Data Requirements

- Chemistry, Manufacturing, and Controls
  - Manufacturing methods, facilities, and controls
    - Full descriptions of methods, facilities and controls for manufacture, processing, and packaging
    - Sponsor facilities and contract facilities included
    - Personnel qualifications
    - Identity, Strength, Quality, Purity
    - Specifications
    - Master formula
    - Labeling operations and controls
    - Analytical controls and sample collection
    - Methods of analysis with adequate sensitivity
    - Special attributes if product purported to be sterile
    - Batch control numbering system
    - Container, closure and other packaging
    - Stability studies
    - Management to preclude contamination
    - cGMP certification

Data Requirements

- Target Animal Safety
  - 21 CFR 514.1 (b) (7), (8)
  - Evidence to establish safety
  - "…contains full reports of adequate tests by all methods reasonably applicable to show whether or not the new animal drug is safe and effective for use as suggested in the proposed labeling."
  - Definitive tests defined by guidelines
  - GFI 185/ VICH GL 43
  - Basic Design
    - 0, 1, 3, 5 X Dose for three times the duration
    - Final formulation
    - Full clinical pathology
    - Full histopathology
    - 4 animals per sex per group

Data Requirements

- Effectiveness
  - "An application may be refused unless it includes substantial evidence of the effectiveness of the new animal drug as defined in § 514.4."
  - "Substantial evidence means evidence consisting of one or more adequate and well-controlled studies, such as a study in a target species, study in laboratory animals, field study, bioequivalence study, or an *in vitro* study, on the basis of which it could fairly and reasonably be concluded by experts qualified by scientific training and experience to evaluate the effectiveness of the new animal drug that the new animal drug will have the effect it purports or is recommended, or suggested in the labeling or proposed labeling thereof. Substantial evidence shall included such adequate and well-controlled studies that are, as a matter of sound scientific judgment, necessary to establish that a new animal drug will have its intended effect."
  - "It is understood that the labeling and advertising for the new animal drug will prescribe, recommend, or suggest its use only under the conditions stated in the labeling which is part of this application…"

Data Requirements

- Effectiveness
  - Pilot work
  - Literature
  - Dose Justification
  - Clinical Field Study
    - Support the label claim being sought
    - Good Clinical Practice Standard
    - Test final formulation
    - Clinically relevant, statistically significant result

Data Requirements

- Environmental Assessment
  - "The applicant is required to submit either a claim for categorical exclusion under § 25.30 or § 25.33 of this chapter or an environmental assessment under § 25.40 of this chapter."
    - § 25.30 - Allows categorical exclusions
    - § 25.33 - Defines for Animal Drugs
      - If exclusion, no need for an EA or EIS
      - "…marketed under the same conditions of approval…"
      - "…intended for non-food animals…"
      - "…minor species…if approved before"
      - "…used under prescription or veterinarian's order…"
      - "…action on an INAD…"
    - § 25.40 - Environmental Assessment
      - Work under NEPA
      - Assessment leads to EI or FONSI
      - Policy then defines the specific testing
      - Basically compatible with VICH

Summary

- Safety, Efficacy, and Quality
- In the US, a new animal drug
- In the EU, a veterinary medicinal product
- Core Agencies:
  - US FDA/CVM
  - EU EMA/CVMP
- Data requirements similar around the world
- Expensive and time consuming process
- Significant investment in time and money