FDA’s innovation initiative to evaluate novel emerging technologies and international cooperation in the area of innovation

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Questions for Consideration

• What agency has jurisdiction?
• What are the evidentiary standards that must be met?
• How can you maximize the value of your early work to help meet the evidentiary standards?
• How can you fully utilize international information/obtain global approval?
Jurisdiction in the U.S.

- FDA/CVM
- FFDCA
- USDA
- VSTA
- EPA
- FIFRA
- FDA/CVM
- FFDCA
- USDA
- VSTA
- EPA
- FIFRA
- FDA/CVM
- FFDCA
- USDA
- VSTA
- EPA
- FIFRA
- FDA/CVM
- FFDCA
- USDA
- VSTA
- EPA
- FIFRA
Jurisdiction: FDA or EPA?

- Memorandum of Understanding Between The Environmental Protection Agency and the United States Department of Health, Education and Welfare, Food and Drug Administration

- SUBJECT: MOU with EPA regarding mutual responsibilities under FFDCA and FIFRA.
Pesticides that are drugs

Certain pesticides subject to the laws administered by EPA are also deemed to be animal drugs and subject to the laws administered by FDA under, but not necessarily limited to, the following conditions:

• i) Products for oral administration such as tablets, boluses, drinking water preparations, medicated blocks, and medicated feeds, including liquid feeds and supplements (these do not apply to articles solely for the control of fecal breeding flies, nor solely for sanitizing the drinking water of animals).
• ii) Products administered parenterally.
• iii) Products which are absorbed through the skin surface as in demodectic mange conditions.
• iv) Products introduced into wound or body openings, except for screwworms control, including application to the ear canal, for the control of ear mites; such conditions often require supportive treatment.
• v) Products applied topically for their systemic action in an animal.
Jurisdiction: USDA or FDA?

• MOU between APHIS/USDA and FDA/HHS
  – procedures and responsibilities for resolving jurisdictional issues/questions

• Determination is based on the primary mechanism of action, and the specific marketing claim made for the product

• Standing Committee – meet at least quarterly
  – Liaison from each agency
    • Donna Malloy APHIS/Vitolis Vengris FDA
    • Three (3) or more people from each agency
  – contact liaison for determination of jurisdiction
  – Decision will be communicated to applicant, in writing, by the agency with the regulatory authority
Regulated as “drugs”

- 1. Antibiotics, including antimicrobial peptides such as alpha and beta-defensins, chemotherapeutics
- 2. Anti-inflammatories (steroidal and nonsteroidal)
- 3. Anthelmintics/Antiprotozoals, except vaccines
- 4. Competitive Exclusion products
- 5. Genetic constructs, excluding DNA vaccines and live vaccines that stimulate a protective immune response.
- 6. Stem cell therapies
- 7. Gene therapies and somatic cell therapies utilizing viral and non-viral vectors
- 8. Hormones, growth factors, growth promotants
- 9. Cytokines administered for systemic or anti-inflammatory effect
Regulated as “drugs”, cont’d

• 10. Cytokines intended to treat mastitis either as (a) stand-alone therapies, (b) in combination with approved antibiotics or (c) any other treatment modalities.

• 11. Cytokines of human origin for human use already regulated under the FFDCA or the Public Health Service Act.

• 12. Cytokines that affect blood cell formation (hematopoiesis, erythropoiesis, myelopoiesis).

• 13. Interferons whose primary mechanism of action does not require stimulation of the immune system.

• 14. Agents or products administered to animals for the purpose of reducing human exposure to pathogens.

• 15. Whole blood, transfusion, and clotting products except serum and plasma products for passive transfer of immunity.
Regulated as biologics

1. Cytokines and/or interferons co-administered (a) with an approved vaccine produced by the sponsor and intended to be an integral component of the vaccine, (b) with an approved vaccine produced by another supplier, or (c) with an approved vaccine produced by the sponsor but not intended to be used exclusively any one product.

2. Localized, including topically administered cytokines where the intent is to affect local immune responses and there is reasonable certainty that administration will not result in systemic circulation of the cytokine.

3. Cytokine nucleotide sequences administered, either as an integral part of a DNA vaccine, or administered as an adjunct to vaccine administration.
Regulated as biologics, cont’d

• 4. Bacteria, viruses, bacterial, and viral-derived products whose intended use is the treatment or cure of cancer in animals by immune mediated mechanisms.

• 5. Bacterial-derived CpG oligonucleotides administered as a stand-alone treatment. CpG oligonucleotides administered as part of a vaccine shall be considered to be an integral part of the vaccine acting as an adjuvant and will be regulated by the Agency with jurisdiction over the vaccine.

• 6. Vaccines, viruses, bacterins, bacterial extracts, allergens, antiserums, antitoxins, toxoids, diagnostics, and immunomodulators for the prevention and/or treatment of animal disease.

• 7. Immunoglobulins, serum, and plasma for passive transfer.
FDA Drug vs. Food

- Intended use of a substance determines if it is regulated as a food or a drug
  - Matrix listing to delineate drug vs. food
Food

- Legal definition – Food is “articles used for food or drink for man or other animals” [21 USC 201(f)]
- Food is made of substances that
  - Provide nutrition (nutritive value), taste, or aroma to the animal
  - Affect the characteristics of food
Food Additive

- Defined in 21 USC 201(s) as “any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component of or otherwise affecting the characteristics of any food.”
  - Section 201(s) excludes any substance that is GRAS or that qualifies for any of the other exemptions from the food additive definition (e.g., new animal drug, color additive, etc.)

- Food additives require premarket approval

- Food additive petition process in 21 CFR 571.1

- Approved animal food additives in 21 CFR 573
Food Additives

- There are several types of food additives, based on composition and intended use, used for purposes such as: nutrient, aroma/flavor, taste, soluble or insoluble fiber, stabilization, emulsification, preservation, anti-oxidant, etc.
- A substance that does not become a component of the food but that is used, for example, in preparing an ingredient within the food to give it a different flavor, texture, or other characteristic may also be a food additive.
Food Additive Petition

• Food additive petition (21 CFR 570 and 571) should address:
  – Safety - to the animal and to humans consuming food products from animals consuming the food additive
  – Utility - intended physical, nutritional or other technical effect
  – Manufacturing chemistry
  – Labeling - cautions, warnings, shelf life, directions for use
  – CVM also evaluates the possibility for environmental impacts to occur
Substance generally recognized as safe (GRAS) for intended use

- Generally recognized as safe (GRAS) (21 CFR 570.30) for a species-specific intended use
  - General recognition of that safety among qualified experts
  - Evidence of safety (based on history of safe use prior to 1958 or scientific procedures)

- More information available at
  - [http://www.fda.gov/animalveterinary/products/animalfoodfeeds/generallyrecognizedassafegrasnotifications/default.html](http://www.fda.gov/animalveterinary/products/animalfoodfeeds/generallyrecognizedassafegrasnotifications/default.html)
  - [http://www.fda.gov/safefeed](http://www.fda.gov/safefeed)
FDA - Animal Drugs

- Regulated under the Federal Food, Drug, and Cosmetic Act (FFDCA)

- Defined by intended use
  
  - articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals
  
  - articles (other than food) intended to affect the structure or any function of the body of man or other animals
ONADEs Vision/Mission

• Expeditiously approve quality safe and effective new animal drug products through a science-based approach in a regulatory environment
  – Employ applicable science to make high quality safety and effectiveness decisions
  – Keep unsafe and ineffective drugs off of the market

• Communicate with our stakeholders and understand the forces that affect them
  – Understand the economics of the animal health industry as it pertains to drug availability

• Protect human, animal, and environmental health and promote a safe and abundant food supply
How we measure success of our public health mission

Put in the hands of the end-user

- approved,
- safe and effective,
- quality manufactured,
- properly labeled

new animal drugs to meet therapeutic and production need of animals
Four Legal Pathways to Market

- An approved new animal drug application (NADA) under section 512 of the FFDCA (Pioneer)
- An approved abbreviated NADA (ANADA) under section 512 of the FFDCA (Generic)
- A conditional approval under section 571 of the FFDCA or (MU/MS)
- An index listing under section 572 of the FFDCA (MU/MS)
New Animal Drug Approval Process
Four Critical Approval Standards

- **Safety**
  - Human Food
  - Target Animal
  - Human User
  - Environmental Impact

- **Effectiveness**

- **Quality Manufacturing**

- **Proper Labeling**
Technical Sections

- Effectiveness
- Target Animal Safety
- Human Food Safety
- Environmental Impact
- Manufacturing Chemistry
- Labeling
- All Other Information
Effectiveness

Substantial Evidence

- One or more adequate and well-controlled studies

- Demonstrate the drug is effective for the intended use at the dose or dose range and associated conditions of use prescribed, recommended or suggested in the labeling
Effectiveness studies, such as

- A laboratory dose confirmation study
- A study in laboratory animals
- Any field investigation
- A bioequivalence study
- Systematic review and meta-analysis
- An *in vitro* study
Target Animal Safety

Adequate tests by all methods reasonably applicable to show that the drug is safe for use under the conditions prescribed, recommended or suggested in the proposed labeling

Includes human user safety
Target Animal Safety studies, such as

- Pharmacologic/toxicologic study
- Margin of Safety Study
- Tissue Irritation Study
- Reproductive safety study
- A bioequivalence study
- Animal Class Safety Study (young, geriatric)
- Special Cases (specific breeds)
Human Food Safety

• **TOXICOLOGY:**
  – determine the no observable effects level (NOEL), acceptable daily intake (ADI), and safe concentration

• **RESIDUE CHEMISTRY:**
  – determine the target tissue, marker residue, slaughter withdrawal, and milk withhold times

• **MICROBIAL FOOD SAFETY:**
  – evaluate the safety of antimicrobials with regard to their microbiological effects on bacteria of human health concern (Guidance 152 and 159)

• **REGULATORY METHOD:**
  – development and validation of methods to measure drug residues in edible tissues
Human Food Safety studies, such as:

**Toxicology**
- Genotoxicity studies
- 2 90-day studies
- Reproductive Study
- Developmental study(ies)
- User safety information
- Impact on Human gut flora
- Additional/Special studies (if needed)

**Residue Chemistry**
- Total residue metabolism and metabolism in target animals
- Comparative metabolism in target and laboratory species
- Analytical methods development and validation
- Tissue residue depletion studies
- Method transfer trial
Human Food Safety

**Microbial Food Safety**

- Impact of the use of antimicrobial new animal drugs (and compounds with antibacterial activity) on the emergence or selection of antimicrobial resistant bacteria in or on treated food-producing animals and subsequently in or on food (GFI #152)

- Impact of the residues of antimicrobial or other NADs in food producing animals on the intestinal flora of human consumers (GFI #159/VICH GL 36)

**Regulatory Method**

- Development and validation of methods to measure drug residues in edible tissues, including a demonstration of transferability
Environmental Impact

National Environmental Policy Act (NEPA)

Requires Federal Agencies to consider environment impact of their actions
Environmental Impact

- Categorical Exclusion or
- Environmental introduction and fate studies
- Environmental effects studies
- Environmental assessment
Chemistry, Manufacturing, and Controls

- sponsors demonstrate that the animal drug will have and maintain the necessary quality, strength, purity, and identity
  - Methods and controls
  - Stability data
  - cGMP compliance
Labeling

- immediate container (vial, syringe, packet) or feed bag labels
- package insert
- packaging (box, carton)
All Other Information

- Drug sponsors must submit all information pertinent to an evaluation of the safety and effectiveness
- received or otherwise obtained by the applicant from any source
- including information
  - derived from other investigations or commercial marketing (for example, outside the United States)
  - reports in the scientific literature, both favorable and unfavorable
Genetically Engineered Animals

- Growing field
- Regulatory framework developed
  - GFI #187 published
- Three approvals
- Demonstrate that there are alternative ways to approve drugs – alternative ways to meet the regulatory standard
GE animal review process

• Hierarchical, weight-of-evidence, risk based
  – AND it Satisfies the statutory requirements for safety and effectiveness
  – Follows NADA regulations with adaptations for technology/expertise
Animal Drug Approval Process

Discovery or Acquisition → Early Development → Full Development → Approval → Support

FDA/CVM

Proof of Concept


Presubmission conference
Agree on development plan

Submissions
Protocols
Studies
Data
Literature
Other Information
Need for New products/drugs

• What drives Discovery?
  – Predict the market 8-10 years out
  – Consumer demand/need
    • Convenience/cost effective/effective
  – Current therapeutic vacuum
  – Resistance to approved products (antimicrobials) and need to discover alternatives
Discovery

• Acquisition
• Partnerships
• Research Collaborations
  – Scientists
  – Academia
  – Veterinary colleges/universities
Questions asked (and answered) in Discovery

- Will the product meet an identified need?
- What is the claim?
- Does it possess desirable
  - Effectiveness – Pharmacologic effects and in which species
  - TAS – toxic endpoints
  - HFS – based on the structure of the molecule/related compounds, is it safe for human food?
  - dosage form
- Can it be manufactured at acceptable concentration and volume for convenient administration at large/commercial scale
- Is it economical?
  - Does it have market value?
  - Are there market differentiators?
- Requires knowledge of current and future markets
Proof of Concept

• Decision point between Discovery and Development

• Management decision (business and scientific) whether or not to move molecule into Development
  – Does this fit into Co. portfolio/strategy
    • Might be a great compound for pigs, but they aren’t in the swine market
  – Does it still have favorable projected marketplace
  – Is the $$ available to pursue approval
Early Development

• Many Small trials to identify any issues
  – Are there unacceptable TAS concerns?
• How does the drug behave in the target animal?
  – Pharmacology (absorption, distribution, metabolism, and excretion)
• Is there enough of an effect to pursue development?
Full Development

• Sponsors are working toward meeting the requirements of the technical sections

• This is when sponsors typically open an INAD file (FDA) and begin communication with CVM
  – Pilot trials
  – Tox trials – HFS
  – Scale up to clinical batches

• Have a presubmission conference to agree on a development plan.
Systematic process to identify knowledge needs, knowledge gaps, and regulatory strategy
Shared Story of Success

Proof of Concept

Development

Approval
CVM Tools to Foster Development of Innovative New Animal Drugs

- **InnoVation Exploratory Team (IVET) Process**
  - Tech Teams
  - Focus Groups
  - IVET VMF files

- Early Information (EI)
Early Information/Tech Teams

- Two processes exist to provide new avenues for earlier exchange of information and dialogue between CVM and drug sponsors.
- The goal of the early information (EI) and tech team processes is to facilitate reaching agreement efficiently regarding some or all of the investigational requirements for approval at a PSC.
- These processes both may involve back and forth discussions or exchange of scientific information for mutual learning.
- These processes are best utilized for different purposes and may have different characteristics.
Early Information

• Available to all sponsors
• Focus is on a single proposed product
• CVM provides earlier answers to sponsor’s specific questions, allowing the sponsor to propose a development plan more acceptable to CVM
• Usually during the INAD process
• For alternatives to antibiotics, can happen prior to opening and INAD
• Example:
  Discussion on novel experimental designs
Tech Team

• Sponsors can request; however, CVM determines the need
• CVM is able to learn along with the sponsor about a new technology reduces the time CVM spends to learn the technology after the INAD is opened.
• Exchange of information
• Team – that develop the expertise
• Example -
  – Drugs using novel technologies
Focus Groups

• internal teams used to address broad topic areas.
• may be technology-focused, such as biomarkers, or process improvements.
• These might be formed based on conversations with a sponsor.
International Collaboration
Utilize Opportunities for International Collaboration

➤ Veterinary Drug Directorate (VDD)
  – Regulatory Cooperation Council (RCC) – simultaneous review VDD and FDA

➤ European Medicines Agency (EMA)
  – meet quarterly, scientist-to-scientist
  – Parallel Scientific advice available

➤ VICH – Chairs, EWGs

➤ Other opportunities for regulator-to-regulator collaboration (MOU/confidentiality agreements with other countries)
Simultaneous Approvals Under RCC

- Currently there are 5 simultaneous approvals
- Imrestor (pegbovigrastim injection)
  - the first simultaneously reviewed and approved animal drug for use in food-producing animals
- Need to submit the same information to FDA and VDD, meetings should involve both agencies
Parallel Scientific Advice

• Allows for collaboration and harmonization between US and other regions’ regulatory agencies in the pre-approval stage

• Facilitates drug approvals by reducing divergent studies for global registrations

• We have had 3 Parallel Scientific Advice meetings with the EMA
ADVENT

• Ad Hoc Expert Group on Veterinary Novel Therapies – EMA
• Similar to CVM’s IVET process
• Current EMA ADVENT groups:
  – Monoclonal antibodies for veterinary use: specific questions to be addressed by ADVENT
  – Stem cell-based products for veterinary use: specific questions on target animal safety to be addressed by ADVENT
Global Plan for a Global Approval

Companies should share global plan for approval

• Leverage opportunities for us to work with our counterparts in other countries
  • Data sharing across regulatory bodies in different countries
  • Single set of studies for approval in multiple counties
  • Maximize the use of existing/foreign data
  • Increasing the consistency of labeling across countries
Global Approvals — *an achievable goal*

- Sileo (dexmedetomidine oromucosal gel)
- Approval date EU — June 2015; US Nov. 2015
- Indication
  - US — for the treatment of noise aversion in dogs
  - EU — for the alleviation of acute anxiety and fear associated with noise in dogs
- Substantial Evidence of Effectiveness
  - Field study
    - 14 clinical investigators in Finland and Germany
    - NO SITES IN THE U.S.
Future for Drug approval for Food Animals

• We continue to have development of new chemical entities in food animals
  – 7 new chemical entities per decade since 1990 for food animals

• We continue to approve new antibiotics and alternatives to antibiotics for food animals
Summary

- There is a path to approval for your product
- Must meet the statutory requirements
- Statutory requirements are set by Congress
- We have processes to help guide you
- Encourage early communication
- Firm is responsible for product development
- FDA ensures products meet the requirements