U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR VETERINARY MEDICINE
OFFICE OF NEW ANIMAL DRUG EVALUATION

# US FDA's Regulatory Pathway for Alternatives to Veterinary Antimicrobials

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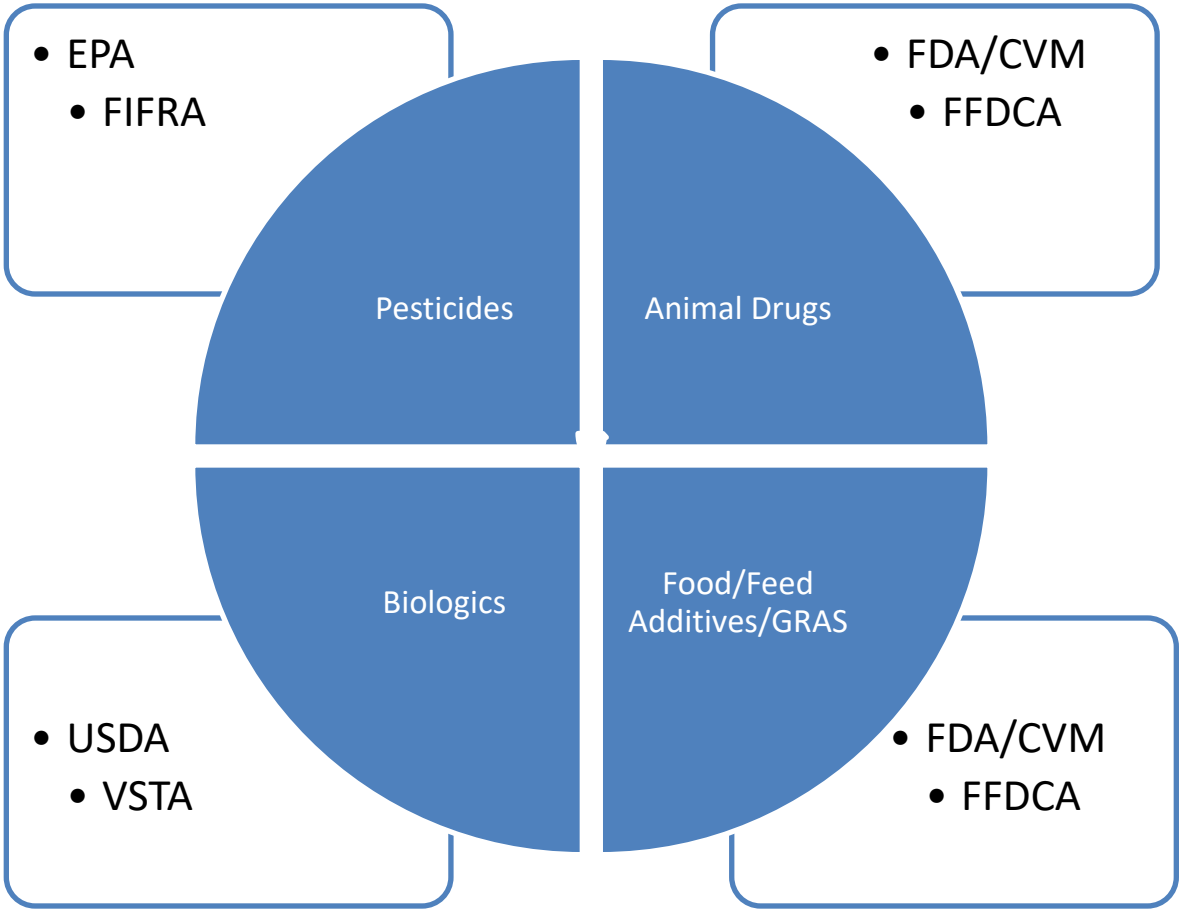
# Jurisdiction in the U.S.

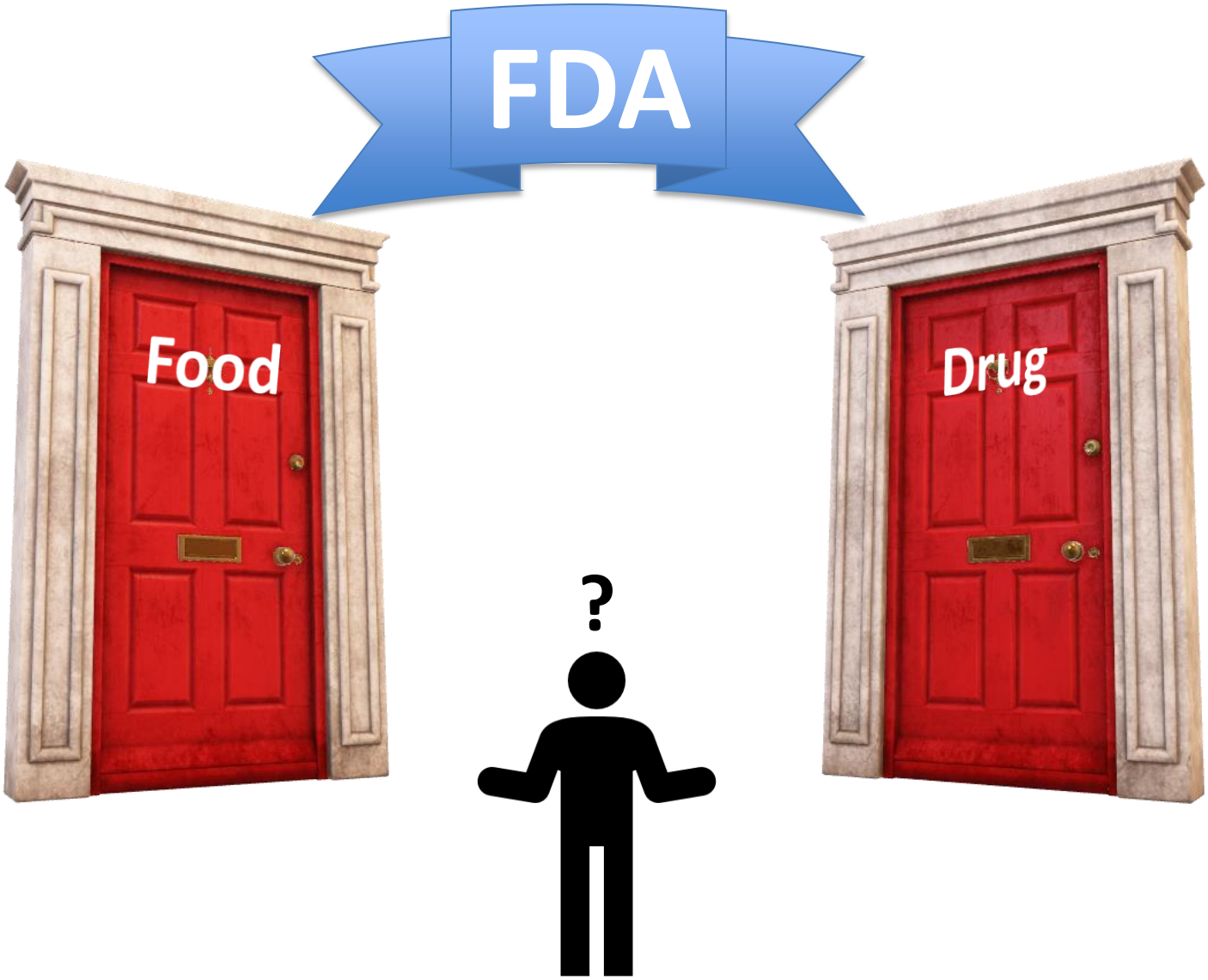


# Regulatory Oversight

- The Agencies will determine who will regulate the product.

- MOU between USDA/CVB and FDA/CVM
  - Considerations may include, but are not limited to:
    - Mechanism of action
    - Intended use
    - Product type (e.g., hormones, peptides, cytokines)

- Don’t make assumptions; ask early.
  - AskCVM@fda.hhs.gov


FDA
Food
Drug
?

# FDA Drug vs. Food

- Intended use of a substance determines if it is regulated as a food or a drug
- CVM Program Policy and Procedures Manual Guide 1240.3605, Regulating Animal Foods with Drug Claims at
  - http://www.fda.gov/downloads/animalveterinary/guidancecomplianceenforcement/policiesproceduresmanual/ucm046883.pdf
  - Matrix listing to delineate drug vs. food

# Food

- Legal definition – Food is “articles used for food or drink for man or other animals” [section 201(f) of the FFDCA ]
- Food is made of substances that
  - Provide nutrition (nutritive value), taste, or aroma to the animal
  - Affect the characteristics of food
  - May directly or indirectly become a component of food through processing, packaging, etc.

# Food Additive

- Defined in Section 201(s) of the Act 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/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"

Therapeutic

Production

# 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
- 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

* Human User Safety is also reviewed under this technical section

# 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

# 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 (Guidances 152 and 159)
- REGULATORY METHOD:
  - development and validation of methods to measure drug residues in edible tissues

For overview, see CVM GFI #3 – "General Principles for Evaluating the Human Food Safety of New Animal Drugs Used in Food-Producing Animals"

# Environmental Impact

National Environmental Policy Act (NEPA)

Requires Federal Agencies to consider environment impact of their actions

# 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)
- Shipper Labeling

# 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

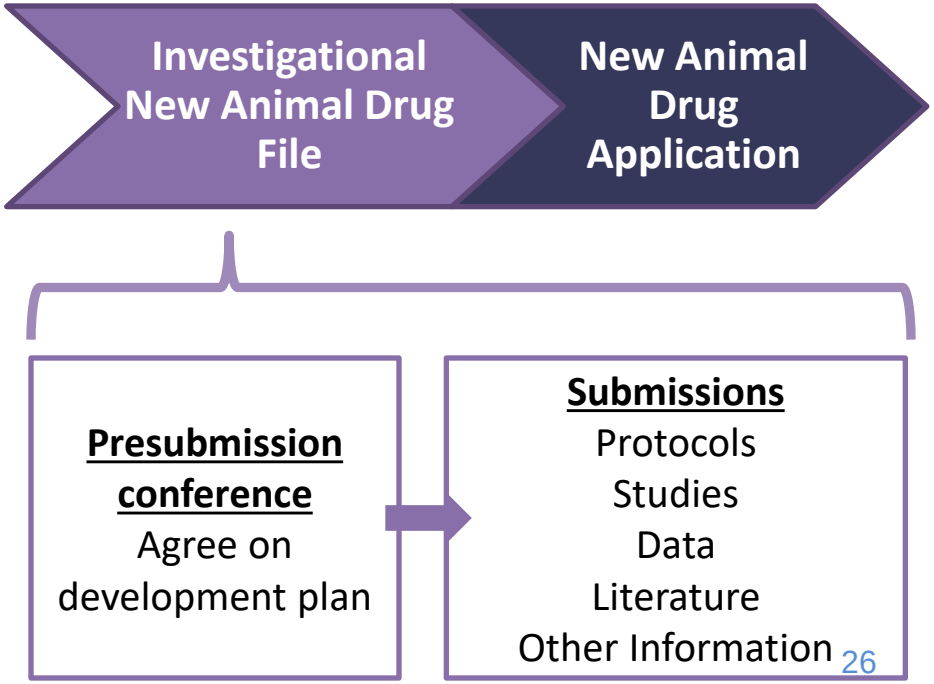
# Regulatory Strategies for Products

- Risk-based, flexible approach
- Same statutory requirements apply, but can require innovative thinking on how to address them
- Early interactions with sponsors
- Guidance/policy development
- Collaboration/communication with other Offices; Centers within FDA
- Communication/Outreach

# Animal Drug Approval Process

**SPONSOR**


**FDA/CVM**



# CVM Tools to Foster Innovative New Animal Drug Review

- Early Information (EI)
- Tech Teams
- Focus Groups

# Early Engagement/Tech Teams

- Exist to provide new avenues for earlier exchange of information and dialogue between CVM and drug sponsors.
- The goal is to facilitate reaching agreement efficiently regarding some or all of the investigational requirements for approval at a PSC.
- May involve back and forth discussions or exchange of scientific information for mutual learning.

# Early Engagement

- 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
- Can happen prior to opening an 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 reducing 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 (e.g., pegylated proteins)

# 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
- May result in advisory documents

# Animal Drug Approval Process

**SPONSOR**

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

**FDA/CVM**

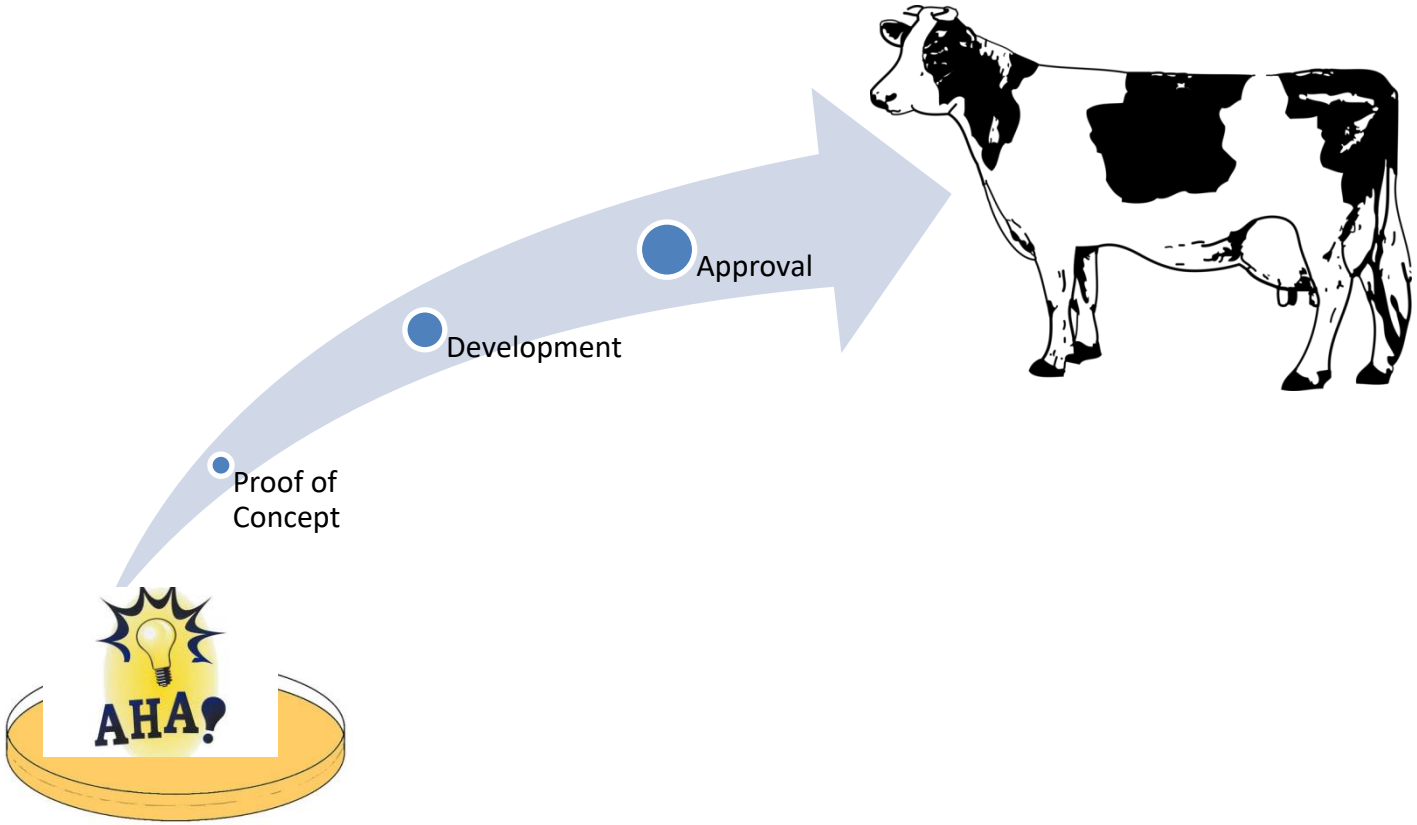
h Team → Investigational New Animal Drug File → New Animal Drug Application

Early Engagement

**Presubmission conference**
Agree on development plan

**Submissions**
Protocols
Studies
Data
Literature
Other Information

# Shared Story of Success



# Select Considerations for Alternatives to Antimicrobials

- User expectations vs. marketing expectations
  - What is the expected effect?
  - How is it proposed to be used?
- Manufacturing the product
  - Can it meet GMPs?
  - Can changes be anticipated?
- Systemic vs. local effects
- Does the product select for subpopulations?
- Residue concerns?

# 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)

# Parallel Scientific Advice

- Feedback on the same set of questions from both FDA and EMA at the same time
- Allows for collaboration and harmonization between US and EMA in the pre-approval stage
- Facilitates drug approvals by reducing divergent studies for global registrations

# 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

- Part of a July 2019 FDA Meeting
  - "Incorporating Alternative Approaches in Clinical Investigations for New Animal Drugs"
  - GFI expected July 2020

# 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

# Incentivizing Development

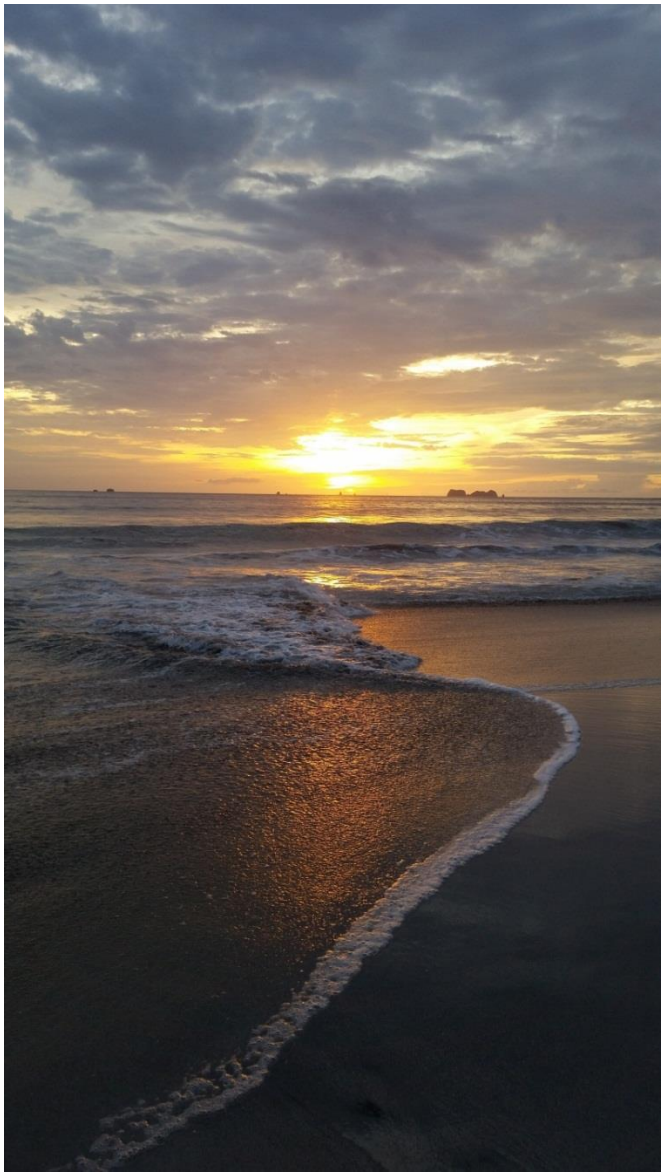
The FFDCA provides for fee waivers and fee reductions:

- Significant barrier to innovation
- Fees exceed costs
- Free choice feeds
- Minor use or minor species
- Small business

Refer to GFI #170 - https://www.fda.gov/media/69918/download

# Summary

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

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