Regulation of Animal Biotechnology at the Food and Drug Administration

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Regulation of GE Animals

- Statutory Authority
- Review Process
Major Statutes Governing GE Animals

Federal Food, Drug, and Cosmetic Act (FD&C Act)
• Products are regulated; not processes

National Environmental Policy Act (NEPA)
• Procedural; orders agencies to evaluate impacts of “agency actions”
History of Regulation of GE Animals in the U.S. Government

• 1986 Coordinated Framework for the Regulation of Biotechnology
  – General overview
  – No new laws/regulations anticipated
  – Allows for “lead agency”/scientific assistance from other agencies

• 2001 case-studies
  http://www.whitehouse.gov/administration/eop/ostp/library/archives

• 2009 Guidance For Industry 187
  – Heritable and non-heritable rDNA constructs
FD&C Act (New Animal Drugs)

• Prohibits introduction of unapproved drug into commerce
  – Drugs are defined as *articles* intended to
    • Diagnose, cure, mitigate, treat, or prevent disease
    • Affect the structure or any function of the body
• Exemption for research
  – Investigation/Investigational Animal
• Sponsor of application must demonstrate
  – Safety to animal
  – Food safety (if animal intended for food use)
  – Effectiveness (does the article do what the sponsor claims?)
Statutory Authority Clarified in Guidance for Industry 187*

• Covers all types of GE animals
  – Heritable and non-heritable rDNA constructs
• Definition of “article”
  – rDNA construct intended to affect the structure or function of the animal
• All GE animals in a lineage are covered
• Event-based, case-by-case evaluation
• Enforcement discretion and approval paths
• New Animal Drug Application (NADA) means mandatory approval prior to marketing
• Post-market surveillance

Regulation of GE Animals: Process

- Real time review
  - Data/information submitted as animals are being developed

- Risk-based cumulative review
  - Weight of evidence evaluation

- Multi-disciplinary
  - within/across FDA centers
  - other agencies in US Government
What is an Investigational New Animal Drug (INAD) file?

- INAD = administrative file, not authorization
- Opens path for confidential communications
- Allows for movement during development
- Outlines obligations and responsibilities
  - Shipments/labeling
  - Record keeping
  - Animal disposition
    - No investigational animals/products in food supply without prior authorization (food safety assessment)
  - First look at environmental considerations
  - Defines qualified investigators/collaborators/CROs
What is an Investigational Animal?

From GFI 85 (VICH Harmonization)
“...any animal that participates in a clinical study, either as a recipient of the investigational veterinary product or as a control”

- Animals known to contain rDNA constructs
- Animals that may contain rDNA constructs (no-takes)
- Surrogate dams
- Female breeding partners of GE males
- Litter mates of GE animals
- Sentinel animals closely co-housed
Case-by-Case Evaluations

An event is the result of the interaction of the rDNA construct with the animal

“All GE animals derived from the same transformation event contain the same article, and subject to evaluation under a single new animal drug application.” (Guidance 187 p 6)

• Each GE Animal/rDNA construct event is considered on a case-by-case basis
  – Specific set of risk questions
  – Specific set of data/information driven responses

• Multiple events covered under single INAD as lineage progenitor is derived.
GE Animals: Products (1)

• Enhanced Food Quality/Agronomic Traits/Environmental Benefits
  – Cows Producing Milk with Long Shelf Life/Digestibility
  – Growth Enhanced Atlantic Salmon
  – Omega-3 Fatty Acid Pork
  – Milk for Cheese Making

• Animal Health
  – Mastitis-Resistant Dairy Cows
  – BSE-Resistant Cattle
  – Other disease resistance
GE Animals: Products (2)

• Products for Human Therapeutic Use
  – Chickens/Cattle/Goats for pharmaceutical production
  – Swine as Xenotransplantation Sources
  – Cattle/Goats producing anti-biowarfare agents

• Mixed-Use High-Value Products
  – Goats producing spider silk
  – Cows producing highly specific
  – antibody:functional molecule products
GE Animals: Products (3)

- Companion Animals
  - GloFish
Hierarchical Risk-Based Evaluation

1. Product Definition
2. Molecular Characterization of the Construct
3. Molecular Characterization of the GE Animal Lineage
4. Phenotypic Characterization of the GE Animal
5. Genotypic and Phenotypic Durability Plan
6. Environmental/Food/Feed Safety
7. Claim Validation
8. Post-Approval Reporting
Product Definition

Describes the animal, construct, and proposed claim as basis for hazard identification.
Molecular Characterization: Construct

Are there sequences likely to contain potential hazards to the animal, humans or animals consuming food from that animal, or the environment? e.g., mobilizeable sequences from viruses endemic in that species?
Molecular Characterization: GE Animal Lineage

Does the insertion of the rDNA construct pose a hazard to the animal, humans or the environment?
Phenotypic Characterization

Direct and indirect risks posed to the GE animal? (e.g., can surveying the health and other phenotypic characteristics of the animal inform us with respect to risk to the animal and potential human food safety concerns?)
Durability Assessment and Plan

Are the genotype or phenotype of the animal changing over the lifespan in a way that would affect the risk(s) associated with the product?

Is there a plan for monitoring stability to anticipate or identify those changes?
Food/Feed Safety

IF INTENDED FOR FOOD/FEED
Risk of direct or indirect adverse outcomes associated with the consumption of the GE animal as food or feed?

IF NOT INTENDED FOR FOOD/FEED
Evidence provided to demonstrate that investigational or post-commercialized GE animals will not enter the food supply?

Method of identity
Environmental Safety

Direct or indirect effects from introduction of the GE animal into the environment?

Basis for satisfying NEPA requirements.
Claim Validation

Does the GE animal meet the claim established in the product definition?
Analytical Method for Identity: Characteristics

- Identifies approved GE animal in mixed population
- Determines if edible tissue is from approved GE animals
- Discriminates approved product from “knock-off”
- Practical in a regulatory laboratory
Regulatory Process Conclusions

• U.S. FDA regulates genetically engineered (GE) animals under FFDCA and NEPA

• Risk-based hierarchical method of review

• Close interaction between FDA and sponsors for a real-time review of submissions
Our First Approval:
GE Goats Producing Human Antithrombin
GE Animals for Biopharmaceutical Production

• Considerations
  – Two regulated articles
  – Characteristics and intended use of second article determine that review

• Goals
  – Risk-based, non-duplicative reviews
  – Coordinated with “Final Product” Center
  – Harmonized data/review requirements
ATryn Goat Approval (2/6/09)

2 Separate Legal Actions

• CVM NADA approval
  – rDNA construct in GE goat to produce rh antithrombin in milk

• CBER BLA approval for ATryn
  – Anticlotting agent for individuals with hereditary clotting disorders in high risk situations
Conclusions for GE Goats Producing rhAntithrombin

• No hazards identified

• Under GTC Management/procedures
  – Safe to the animal
  – Food/Feed Safety addressed (not for food)
  – Safe for the environment

• Effective
  – rhAT in the milk
Links to the Website

• GE Animals

http://www.fda.gov/animalveterinary/developmentapprovalprocess/geneticengineering/geneticallyengineeredanimals/default.htm

• Cloning

http://www.fda.gov/AnimalVeterinary/SafetyHealth/AnimalCloning/default.htm
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http://www.fda.gov/AnimalVeterinary/default.htm