FDA’s Regulation of Intentional Genomic Alterations in Animals Using Genome Editing

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Potential Uses of Genome Editing in Animals

• To enhance production/food quality traits
• To improve animal health (e.g., disease resistance)
• To produce products intended for human therapeutic use (referred to as “Biopharm animals”)
  – Animals for pharmaceutical production
  – Animals for production of tissues for xenotransplantation
• To develop animal models of human disease
• To control human disease transmission
• To enrich/enhance the animals’ interactions with humans (e.g., allergenicity)
New Animal Drug (NAD)

  – Definition of “drug”: article (other than food) intended to affect the structure or any function of the body of man or other animals
  – Definition of “new animal drug”: any drug intended for use for animals other than man

• For approval, NAD application should demonstrate:
  – Safety, target animal and food safety (if applicable)
  – Effectiveness (ensure the article meets the claim)

• An NAD is considered adulterated if it is marketed without FDA approval
Guidance for Industry 187

• Original Guidance issued in 2009: “Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs”

• Definition of “article”
  – Recombinant DNA construct intended to affect the structure or function of an animal = new animal drug

• Intentional genomic alterations may be heritable or non-heritable (e.g., gene therapy)

• For heritable alterations, regulation applies to the intentionally altered genomic DNA in both the founder animal and the subsequent lineage of animals
Draft Revised Guidance for Industry 187

• Issued in January 2017 for public comment: “Regulation of Intentionally Altered Genomic DNA in Animals”

• Scope expanded to animals whose genomes have been intentionally altered = “IGA animals”
  – random (i.e., using recombinant DNA technology) or targeted DNA sequence changes
  – specific changes (i.e., using genome editing or other technologies)

• For detailed description: https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM113903.pdf
Regulation of Intentional Genomic Alterations to Animals

• Currently 3 NAD applications approved
  – Genetically engineered animals containing heritable recombinant DNA, including those intended to produce human therapeutics
  – e.g., Biopharm goat (2009), Biopharm chicken (2015)

• Flexible, risk-based regulatory framework based on science
New Animal Drug Review Process

• Product definition
• Product characterization
  – Molecular characterization of the alteration
  – Molecular characterization of the animal lineage
• Phenotypic characterization
• Genotypic/phenotypic durability assessment and plan
• Environment safety
• Human food safety/feed safety
• Claim validation/effectiveness
Product Lifecycle Review

Pre-INAD
- First Contact
- Discovery/ Information of Proof of Concept
  - Jurisdiction Determination
  - Regulatory Pathway Determination

INAD
- Product Development
  - Presubmission Conferences
  - Requirement for Technical Sections

NADA
- Approval and Marketing
  - Post-Approval Reporting Requirements

Other FDA Centers*

*For “Biopharm animals“, NADA approval is generally required prior to the human product approval as the animal is part of the “manufacturing process” for the human product.
Safety Concerns for IGA Animals

• Off-target genome editing
  – Off-targets may vary in different animals, cell types, etc.
  – Multiple off-target prediction/detection methods
  – Challenges for thorough evaluation of potential off-targets and data analysis

• Unintended consequences of on-target editing
  – e.g., animal safety issues with myostatin-edited animals

• Germline alteration: unknown long term effects

• Other safety concerns
Considerations for IGA Animals

• Product Definition/Characterization
  – What is the intended use? Used for food production?
  – What is the intended genomic alteration?
  – How is the alteration made? Methods to introduce the intended alteration, including the materials used?
  – How is the alteration evaluated?
  – How are the potential off-targets evaluated?

• Animal Safety
  – Adverse events due to unintended off-target(s)?
  – Unintended biological consequences of on-target alteration(s)?
  – Immunogenicity?
Considerations for IGA Animals

• Environmental/Food Safety
  – Level of animal containment?
  – Impact on the environment?
  – What are the risks/consequences for interaction with wild populations?
  – Toxicity?
  – Allergenicity?
  – Is there an analytical method(s) in place to detect IGA animals from non-edited animals if needed?

• Genotypic/Phenotypic Durability
  – Durability plan to demonstrate the alteration is stable over time
CVM Contact Information

When?
- Early in development/proof of concept studies
- General discussion
- Jurisdiction determination
- Make a recommendation as to whether/when the sponsor should open an INAD or submit to a Veterinary Master File
- Walk you through general regulatory obligations and responsibilities

Who?
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Concluding Remarks

- Animals whose genomes have been intentionally altered, including heritable alterations, are regulated using a flexible, risk-based regulatory approach to ensure safety to human and animal health
- Recommend early communication with CVM
- Collaborative evaluation within FDA centers and government agencies