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)

- Federal Food, Drug, & Cosmetic Act (New Animal Drug Provisions)
  - 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

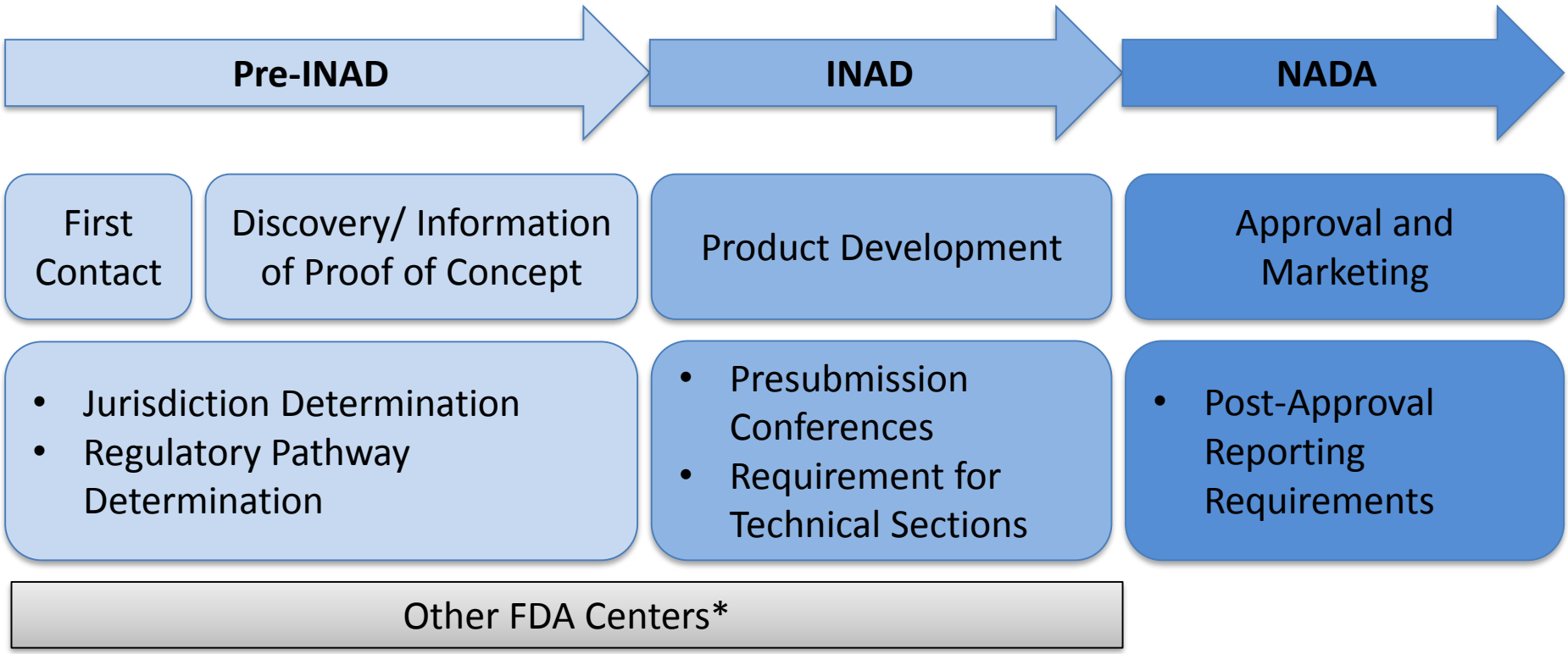
- Currently 3 NAD applications approved
  - Genetically engineered animals containing heritable recombinant DNA, including those intended to produce human therapeutics
  - e.g., Biopharm goat (2009), Biopharm chicken (2015)

- 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



*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


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