FDA's Risk-Based Assessment of Intentional Genomic Alterations (IGAs) in Animals

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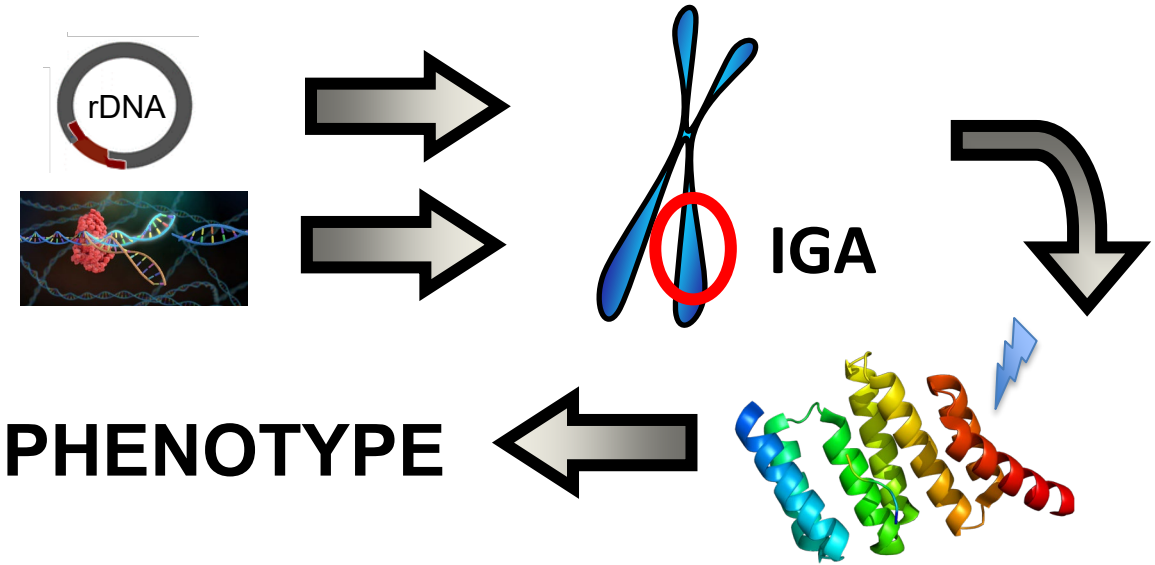
What is an IGA?

- An **IGA** is an intentional genomic alteration introduced into the animal's genome using recombinant DNA, genome editing or other technologies.



An IGA can impact gene/protein expression to produce a desired phenotype.

Regulatory Objectives

FDA review of the IGA is focused on safety:

- Safe to the animals
- Safe to anyone that consumes food from the animals
- Safe to humans
- Does what it claims to do

Hazards of Genetic Engineering

- Hazards may be grouped into 3 broad groups:

Unanticipated Consequences of Intended IGA	Unintended Alterations	
	At Target Site	Elsewhere in Genome
• Net effects of genes with multiple functions • Selective pressure • Impacts of random insertion of transgenes	• Large deletions • Structural rearrangements • Unwanted integration events	• Indels, including large deletions • Structural rearrangements • Unwanted integration events

- The presence of unanticipated consequences or unintended alterations does not inherently present a safety concern; risks are assessed considering all relevant factors and information.

Why do these matter?

- Potential Hazards of IGAs in Animal Agriculture
  - Unintended phenotypic impacts may offset gains in production efficiency, health, or welfare
  - Unintended on-target alterations may mean that the intended alteration may not be consistently integrated across animals or inherited across generations
  - Unintended off-target alterations could lead to propagation of deleterious or insidious traits, amplified by widespread adoption of an IGA

Risk-Based Review Process

The scope of FDA's review process is based on the product's risk-profile:

Approval application not expected based on evaluation of risk factors (enforcement discretion)

Example: IGAs in non-food laboratory animals

Example: IGAs in food producing animals same as conventional animal agriculture with history of safe use

Example: IGAs in food producing animals with human health claims

Risk Characterization

- FDA characterizes and assesses risk for all products reviewed, considering:

Category	Risk Questions
Molecular Characterization	Is the IGA present, and are there any hazards associated with its introduction (including from unintended alterations)?
Phenotypic Characterization (Target Animal Safety)	What is the impact of the IGA on animal health/safety?
Food Safety	What are the risks (if any) of effects associated with consumption of edible products derived from animals with the IGA?
Environmental Impact	If FDA allows the animal with the IGA to be marketed, what is the impact on the environment?

Risk Characterization

- Data expectations vary depending on product- and use-specific considerations

Type of Decision	Review Focus
Enforcement Discretion	Safety: risk to humans (including food safety), animals, and the environment
Approval	Safety and effectiveness: risk to humans (including food safety), animals, and the environment, plus durability (consistency of genotype), post-approval commitments, and effectiveness
Investigational Food Use Authorization	Impacts of entry of proposed number of animals with IGA into food supply

Application Review Process: Risk Characterization

Product Characterization

- Is the IGA present?
- What are the hazards associated with introduction of the IGA in the animals?
  - Are there any unintended alterations that might impact safety?

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- Are the genotype and phenotype consistent over the lifespan of the product?
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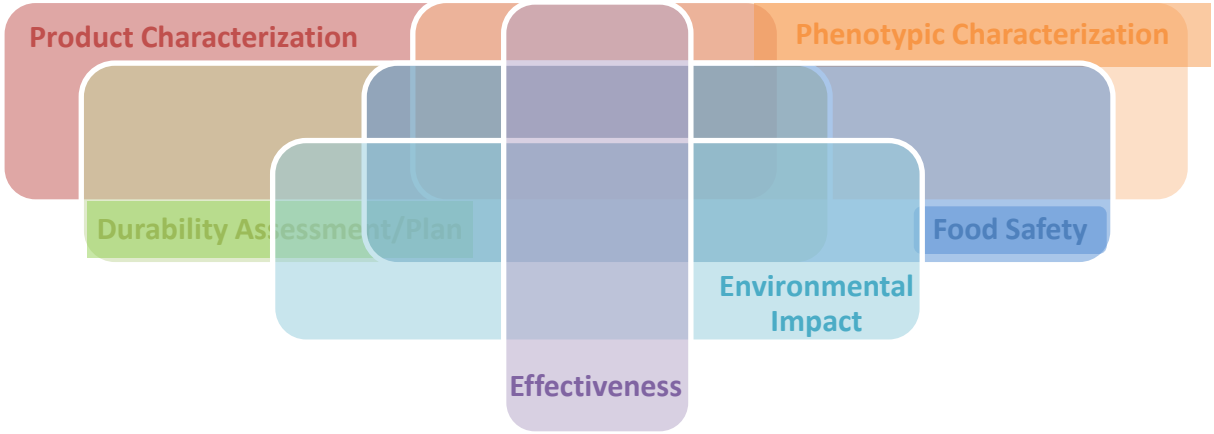
- Does the IGA do what it is intended to do?

Leveraging Data



Approvable Product

Veterinary Innovation Program (VIP)

- Available for animal biotechnology products that provide a benefit to animal or human health, food production, or animal well-being
- Over 50 products enrolled (including 18 IGAs in animals)

Benefits:
- VIP Toolkit
- Frequent Interaction: Meetings Early and Often
- Dedicated Review Team
- Alternative Data Discussions
- CVM Senior Management Involvement
- Feedback on Assay Development
- Pre- and Post-review Feedback
- Stopping/Re-starting the Clock
- Hands on Help with Post-approval Requirements

CVM's Specific Areas of Interest for NASEM Report

- Comparison of methods for generating heritable genetic modification and methods for characterizing intended and unintended alterations
- Species-specific concerns or limitations in technology, including introduction of genetic modification and characterization methods (e.g., availability of suitable reference genome or quality of annotation)
- Plausibility of harm resulting from potential hazards (such as from unintended alterations)
  - Including risk to target animal, humans or animals that consume food from the animal, and the environment
- Plausibility of horizontal gene transfer (e.g., transfer of genetic material from target animal to other organisms in gut or environment)

CVM Contact Information

For general inquires, send an email to: AskCVM@fda.hhs.gov

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