U.S. FOOD & DRUG ADMINISTRATION

Guidance for Industry #187A and B: Heritable Intentional Genomic Alterations (IGAs) in Animals

NASEM Board on Agriculture and Natural Resources

Food and Nutrition Board

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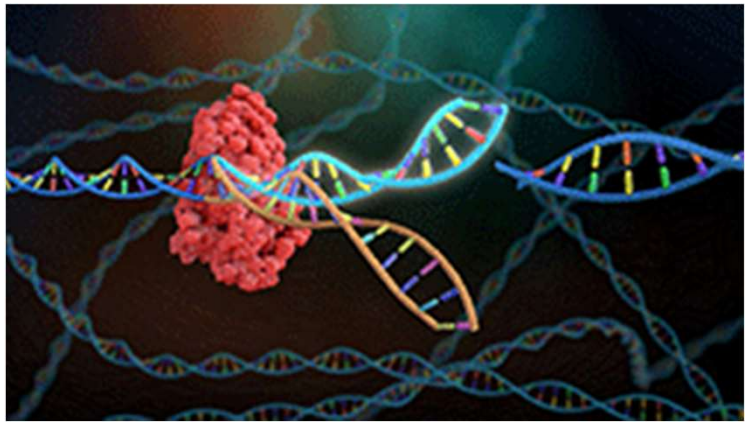
Overview

This presentation will cover:

- GFI history
- Risk-based approach
- Key process elements
- Approval process for IGAs in animals, including pre- and post-

Committee's task: methods for modifications and identification of risks and health hazards to humans, animals, and the environment.



Historical background

- 2009: Final GFI #187 on heritable rDNA constructs in Genetically Engineered (GE) animals
- 2017: Draft revised #187
  - Clarified scope includes all “intentional genomic alterations” or IGAs in animals created using any technology (e.g., rDNA or editing)
- 2024: Final #187A and draft #187B
  - #187A: Broad overview/Risk-based approach
  - #187B: Approval process

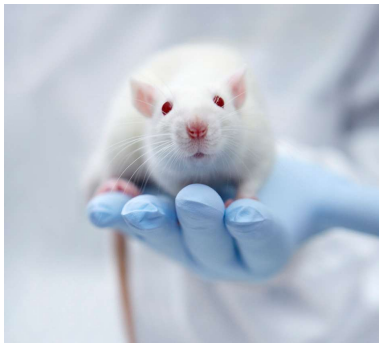
General approach

What are we regulating?

- Specific DNA alteration at each site in the genome where the alteration occurs
  - Legal Authority
- Review includes unintended on- and off-target alterations
  - Cause for concern?

Risk-based approach for IGAs

Three categories:



Category 1: No application expected, no prior review

Category 2: No application expected following prior review of risk factor data

Category 3: Approval application is expected

Category 1

- No application expected; no prior review
- This category has remained the same since the 2009 version of GFI #187; applies to IGAs in certain non-food animals
- Examples:
  - IGAs in animals of nonfood-producing species that are regulated by other Federal government agencies or entities, such as insects with intentionally altered genomes that are regulated by USDA Animal Plant Health Inspection Service
  - Animals of non-food-producing species that are raised and used in contained and controlled laboratory conditions for research (e.g., laboratory mice and rats)

Category 2

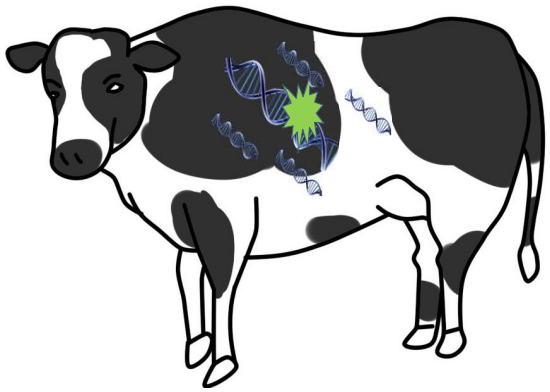
- No application expected following prior review of risk factor data
- What are we determining?
  1. Understand product's risks
  2. Any identified risks are appropriately mitigated; and
  3. No further questions for which we would need to see additional data
- Bottom line: we understand the product's risks and have no safety concerns

Category 2: Changes from prior GFI

- Previously excluded IGAs in animals for food use
- Now, two additional types of IGAs in food animals:
    1. History of safe use
    2. Could theoretically be created with conventional breeding
- Other IGAs: in previous GFI but some modifications

Category 2: History of safe use

- Equivalent to genomic sequences that are found in animals of the same species; and
- History of safe use in animal agriculture food production
  - Sequence and trait in conventionally-raised species and population of food-producing animals with history of safe consumption (e.g., not pot-bellied pigs)



Category 2: Achievable with conventional breeding

- IGA equivalent to what conventional breeding could theoretically achieve;
- No expected food composition changes;
- Intended use doesn't include effects on disease or other health outcome; and
- IGA has no identified risks of concern to humans, animals, or the environment for the intended use.
- Excludes insertion of transgenes

Category 2: Other IGAs

- This category was in previous version of 187
  - Fluorescent aquarium fish
  - Animal models of disease
- As we learn more and technology advances, more IGAs may fit in this category; data expectations may lessen
- Risk considerations:
  - Human
  - Animal
  - Environmental; similar to NEPA review

Category 2: Basis for determination

- Methodology for generating IGA
- Characterization
  - Unintended effects? If so, consequences?
- Animal safety
  - Harmful physical/behavioral changes, disease susceptibility
- Food safety
  - Relevant changes? (e.g. new or different levels of protein, hormone or nutritional changes, etc.)
- Human safety (where relevant)
- Environmental effects
  - No federal action for NEPA purposes but we consider environmental impacts in our evaluation.

Category 2: Getting started

- Veterinary Master File (VMF)
  - For risk review, open a VMF for communications, submissions. No fees.
  - Reach out to CVM early to discuss appropriate regulatory approach and data expectations.
- Veterinary Innovation Program (VIP)
  - Request enrollment
  - Open to most IGAs (not all, e.g. phenotypic traits not related to health/well-being)
  - Benefits assist developers, particularly smaller, unfamiliar w/ FDA regulation

Category 2: What comes next

- Shipping notices
- Investigational Food Use Requests (to put animals into food supply pre-determination)
  - Focus on food safety
- Category 2 Risk Review Request
  - Timeline
    - » 180 days; VIP/stop clock can affect timeline
- Registration and listing
  - Register facilities used to develop IGA; farmers do not register or list.

Category 2: Other considerations

- USDA requirements
  - Labeling
    - » Food Safety Inspection Service labeling regulation
    - » "Bioengineered" labeling – USDA Agricultural Marketing Service
  - Slaughter
- Breeding
  - Farmers/growers do not need to notify FDA to breed animals with risk-reviewed or approved IGAs

Category 3: Approval

- Disease/health claims
- Animals intended for release
- IGAs not in Category 2, including other IGAs for food use
  - Can request risk review for IGAs not already in Category 2 but if FDA does not find it understands risks/has further questions then Category 3

Key points from draft GFI #187B

Article = specific intentional DNA alteration at each site in the genome where it occurs

187B clarifies that:

- Each specific IGA is a separate regulated article subject to approval requirements.
- Multiple IGAs or lines of animals of the same species can be covered under a single file and application.
- There are no additional regulatory requirements to breed animals containing different approved or risk-reviewed Category 2 IGAs with each other (or with animals without IGAs) so long as no new claims are made related to the IGA(s).

IGA product development lifecycle

The product development lifecycle for IGAs can be viewed in four phases:

1. Pre-investigational development (PID): Early research & development, proof-of-concept studies, initial experimental work under a veterinary master file (VMF)
2. Investigational development: Investigational use to generate data in support of approval under an investigational file; typically, under the phased review process
3. Approval: Submission of administrative application after completion of technical sections from phased review process
4. Post-approval: Marketing of product and adherence to post-approval recordkeeping and reporting requirements as outlined in conditions of approval and under 21 CFR 514.80

Product lifecycle highlights

Data and information can be leveraged across the product lifecycle.

PID:

- Request to open a VMF*
- Animals may be shipped for research purposes
- Animals may not be introduced into the food supply without FDA authorization
- Reporting

Phased review:

- Request to open an INAD±
- Studies conducted to support approval
- Animals may be shipped for research purposes
- Animals may not be introduced into the food supply without FDA authorization
- Reporting

Approval:

- Request approval of NADA
- Establishment register the appropriate facilities
- List the product

Post-approval:

- Reporting of durability, morbidity and mortality data and adverse events as outlined in durability plan
- Ongoing unless approval is terminated by sponsor

* There are no fees for VMFs.

± Establishment of an investigational file (INAD) will mean you are a "sponsor" under Section 739 of the FD&C Act and are responsible for payment of an annual sponsor fee unless you are eligible for a fee waiver.

Investigational Food Use Authorizations (IFUAs)

- Developers may request; allows introduction of investigational animals with IGAs into the human or animal food supply.
- IFUAs are for all treated investigational animals.
  - Animals that contain an IGA are considered treated. Animals that are not considered treated include animals that do not contain an IGA, such as surrogate dams in swine, cattle, sheep, and goats.
- For animals subject to slaughter inspection by the USDA's Food Safety and Inspection Service (FSIS), we will inform FSIS if the regulatory criteria are met and we grant an IFUA.

Environmental considerations

NEPA: For major federal actions, FDA must assess environmental impact. Environmental assessments (EA) required unless a categorical exclusion (CatEx) from the requirement to prepare an EA applies.

CatEx requests:

- Submit soon after opening an investigational file
- Includes information on animals with the IGA and containment

EA:

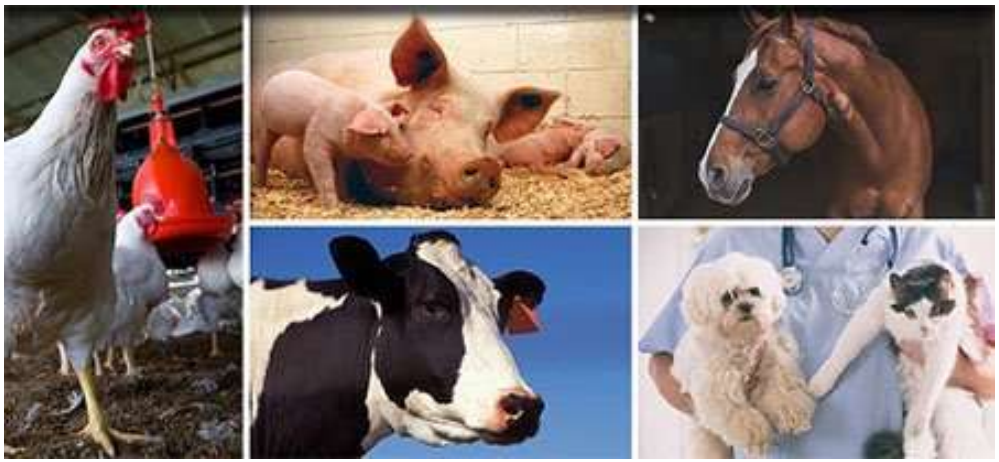
- Submit draft assessment on whether the approval will result in significant impacts on the human environment
- Leads to a Finding of No Significant Impact (FONSI) or preparation of an Environmental Impact Statement (EIS)

Summary of What's new in GFI #187B

- One file can cover multiple alterations
- Recommend data from at least 2 generations but where multiple generations but where not feasible, will consider alternatives.
- Surrogate dams don't need IFUA.
- Farmers/growers, etc. can engage in ordinary activities like breeding.
- Sponsor responsibilities like reporting, registration, etc. do not belong to farmers/producers.
- Even for sponsors, some post-market requirements may not be appropriate based product risks and characteristics; if so, FDA may not enforce.

Conclusion

- Goal: FDA committed to furthering an efficient, science-based regulatory process that enables safe products to reach consumers
- Experience over 20 years has influenced GFI/reviews; will continue to do so
- Open to constructive feedback; continual improvement

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