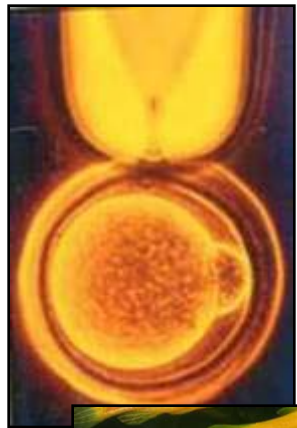


FDA's Regulation of GE Animals: Environmental Issues

Larisa Rudenko and Eric Silberhorn
US Food and Drug Administration
Center for Veterinary Medicine
Animal Biotechnology Interdisciplinary Group

International Symposium on Genetic Biocontrol of Invasive Fish
Minneapolis, MN
June 21-24, 2010





First, a few nomenclature issues.....

“Statute” v

“Regulation” v

“Guidance”

Law:
FFDCA,
NEPA

Helps implement
the law; has force
of law → CFR

Agency’s best
thoughts at the
time; “advice” →
GFI

Colloquial, by many others, esp EU

By US Regulatory Agencies (FDA,
USDA, others?)

Genetically “modified”

Any changes by
the “hand of man”

Genetically “engineered”

Uses rDNA technology



Animal & Veterinary

Email this page Print this page Change Font Size

Home > Animal & Veterinary > Development & Approval Process > Genetic Engineering

Development & Approval Process

Genetic Engineering

Genetically Engineered Animals

Genetically Engineered Animals



Introduction

Genetic engineering is a targeted and powerful method of introducing desirable traits into animals using recombinant DNA (rDNA) technology. DNA is the chemical inside the nucleus of a cell that carries the genetic instructions for making living organisms.

In January, 2009, the Food and Drug Administration issued a final guidance for industry on the regulation of genetically engineered (GE) animals. The guidance explains the process by which FDA is regulating GE animals and provides a set of recommendations to producers of GE animals to help them meet their obligations and responsibilities under the law. While the guidance is intended for industry, FDA believes it may also help the public gain a better understanding of this important and developing area.

What is FDA Doing?

Final Guidance Released 1/15/2009

- FDA Issues Final Guidance on Regulating Genetically Engineered Animals
- CVM GF1 #187 Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs (PDF - 128KB)
- Fact Sheet
- General Q&A
- FDA's Response to Public Comments
- Genetically Engineered Animals Diagram
- January 15, 2009 Transcript for FDA's Media Briefing on FDA's Release of a Final

GE Animal Guidance



Final 1/15/2009

Guidance for Industry #187 - Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs

<http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/GeneticEngineering/GeneticallyEngineeredAnimals/default.htm>

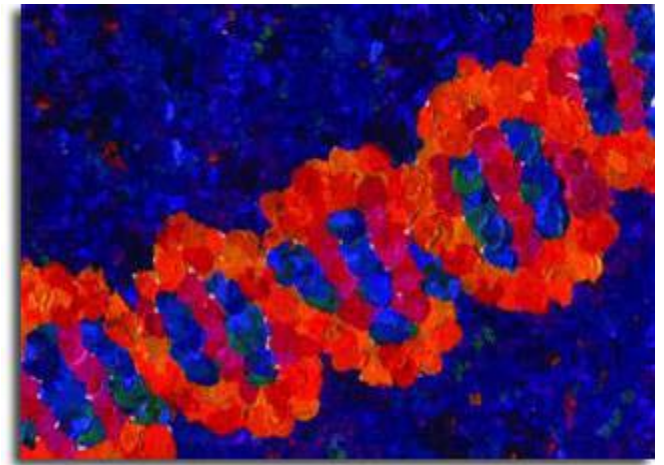
Scope



- All GE animals covered
- Enforcement discretion possible for low risk applications
- INAD/NADA processes
- Post-approval responsibilities

Key Concepts -1

Statutory/Scope



- Definition of “article”
 - rDNA construct intended to affect the structure or function of the animal
- *“All GE animals derived from the same tx event contain the same article, and subject to evaluation under a single new animal drug application.”* (Guidance 187 p 6)
- No products in commerce without FDA approval (minor exceptions → enforcement discretion)

Key Concepts -2

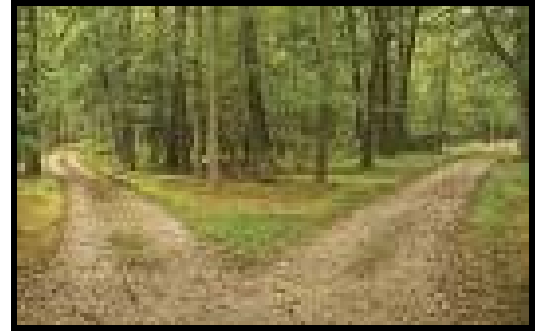
Risk-Based Approach



- Each GE Animal/rDNA construct event poses unique risk(s)
 - Specific set of risk questions
 - Specific set of data/information driven responses

Case-by-case evaluation for each transformation event (i.e., each “article”)

Two Paths



- Default assumption: INAD/NADA approach
 - All species traditionally consumed as food
 - All scenarios not considered “low risk”
- Certain low risk scenarios may be eligible for enforcement discretion (ED)

Which Animals Can Follow the Enforcement Discretion Route?

- For GE animals of non-food species:
 - Regulated by other USG entities
 - Raised/used in contained/controlled conditions
 - GE laboratory animals used in research institutions
- Based on specific ***low-risk*** profile
 - *Zebra danio* aquarium fish genetically engineered to fluoresce in the dark (GloFish)



Environmental Review: The Four Questions

- Does article itself pose human, animal, or environmental risk?
 - e.g., sequences causing human/animal disease, intrinsically or by recombination?
- Does GE animal pose more environmental risk than its non-GE counterpart?
- Does GE animal disposition pose human, animal, or environmental risks?
- Other safety questions?



The background of the slide features a stylized world map in white and light blue, centered on a blue sky with soft, white clouds. The bottom portion of the slide is a solid green field, suggesting a natural or agricultural setting.

Environmental Safety Assessment for the Approval Pathway

The NADA/INAD Review Process aka “Ziggy”

Hierarchical, weight-of-evidence, risk-based

- Satisfies statutory requirements for safety, effectiveness
- Follows NADA regulations, with adaptations for technology/expertise
- Team-based review in new matrixed group



Statutory/Regulatory Requirements

- Sponsor must submit Environmental Assessment/supporting data under INAD/NADA
- National Environmental Policy Act (NEPA) requirement triggered by “agency action”
 - EA → FONSI? (finding of no significant impact)
 - If no FONSI, EIS (environmental impact statement)

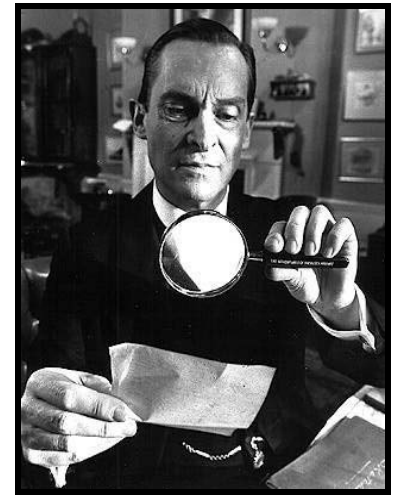


GE Animal: Investigational Use

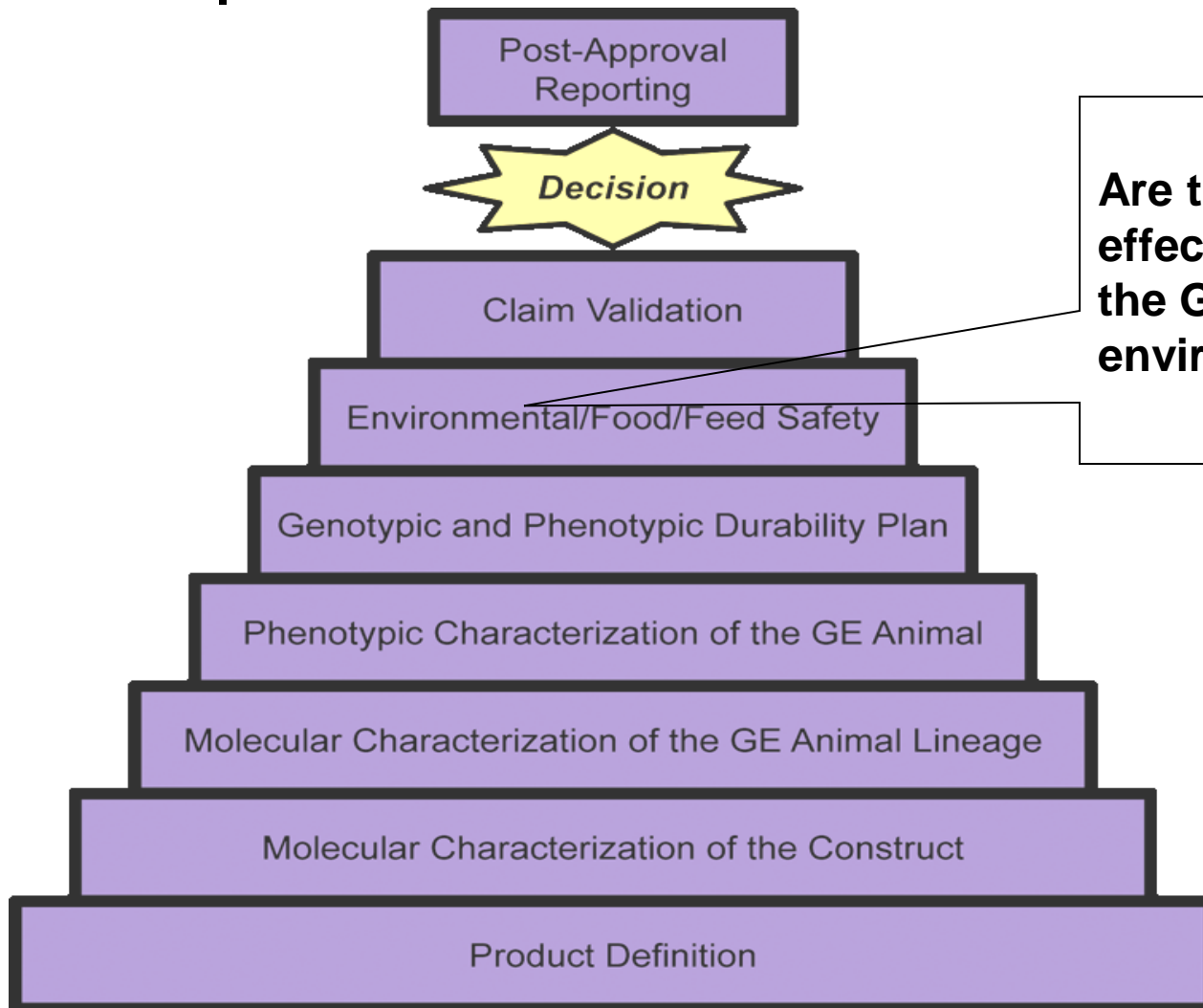
INAD = file; not authorization

Governs certain activities during development

- Animal (drug) shipments/labeling
- Record keeping
- Disposition
 - No investigational animals/products in food/feed supply without prior authorization
- First look at environmental considerations
 - EA under INAD
 - Limited investigations under strict containment
- Qualified investigators/collaborators



Environmental Safety



Are there direct or indirect effects from introduction of the GE animal into the environment?

Environmental Assessment: General Risk Questions



For a specific GE animal (population) containing a specific rDNA construct....

- Risk(s) under conditions of use/free release?
- Likelihood of escape/free release?
 - Containment/redundancy
- Potential [adverse] outcomes associated with escape/free release?

Considered in context of appropriate comparator



What is the Appropriate Comparator?

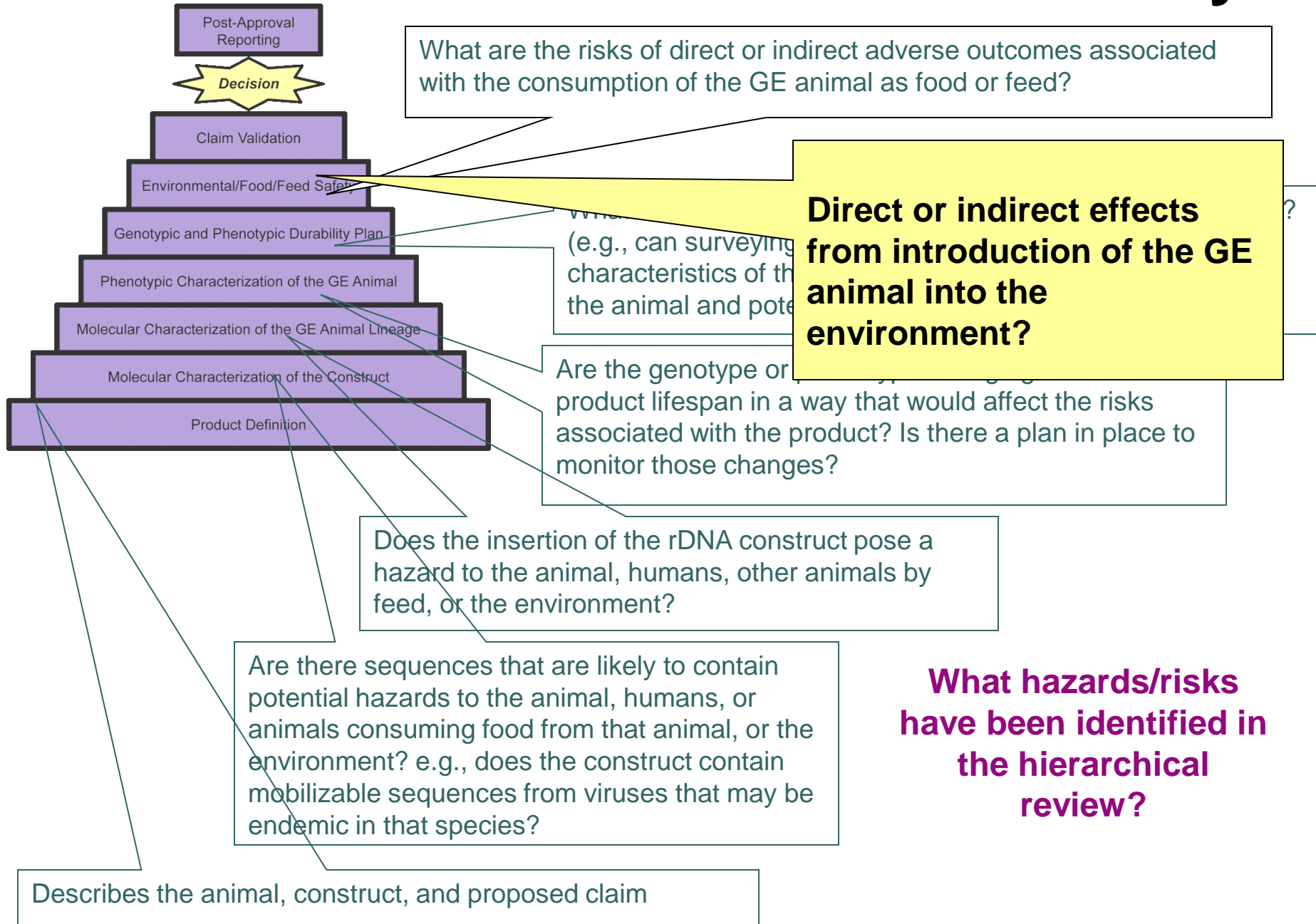
- Case-by-case determination
- Depends on proposed conditions of use
 - If concern is “escape”
 - May be useful to look at “farmed” equivalents
 - May rely on “wild” context
 - If concern is “release”
 - Look at most closely related wild relative
 - More careful look at other (non-target) components of ecosystem
 - May have more modeling, data from close relatives



BUT!

- Can't get to environmental review until other components of hierarchical review done
- R&D and “release” phases generally involve winnowing to a particular “lineage”
- Approvals can start narrow and widen with supplements.

Environmental Safety



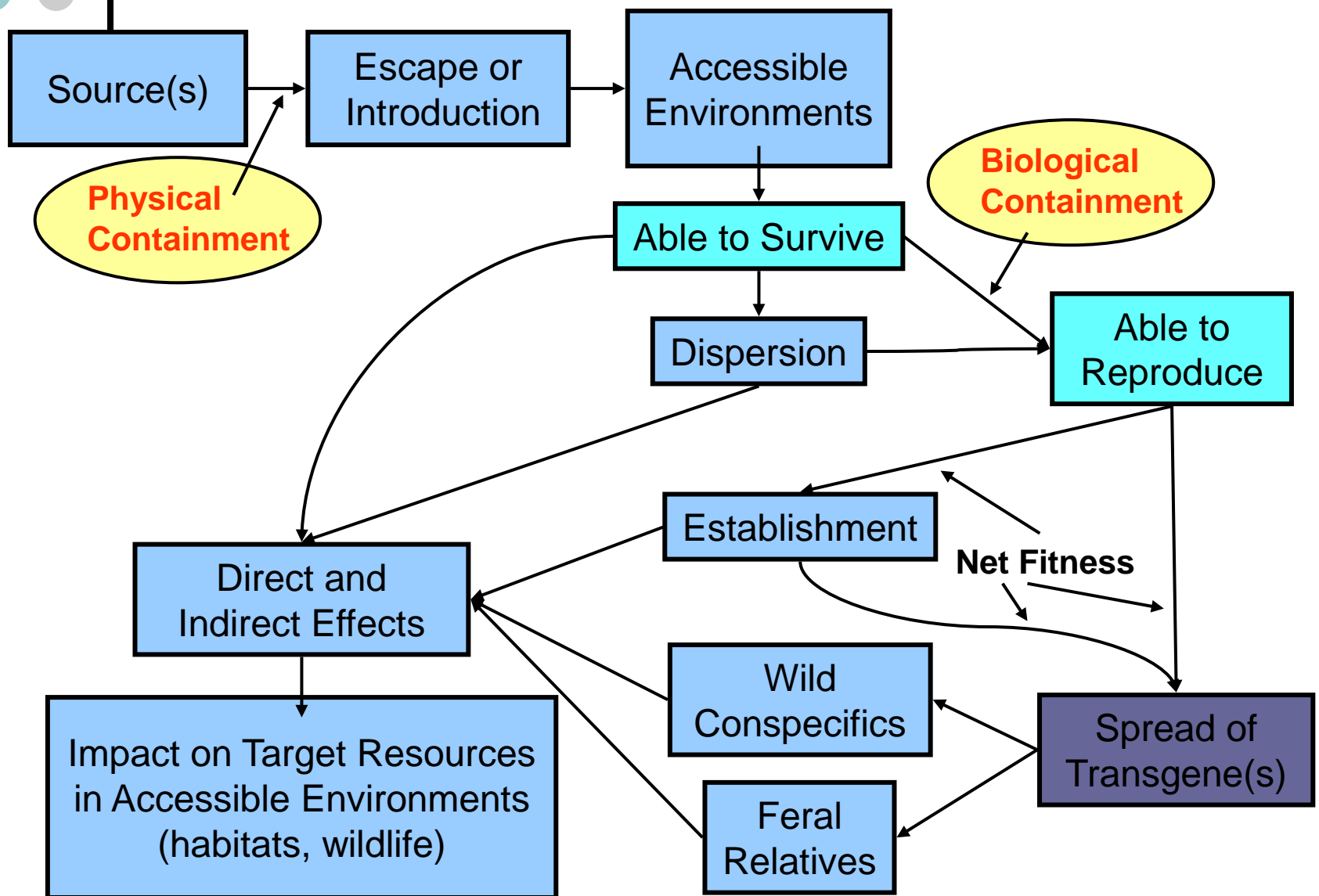


Prioritizing Concerns

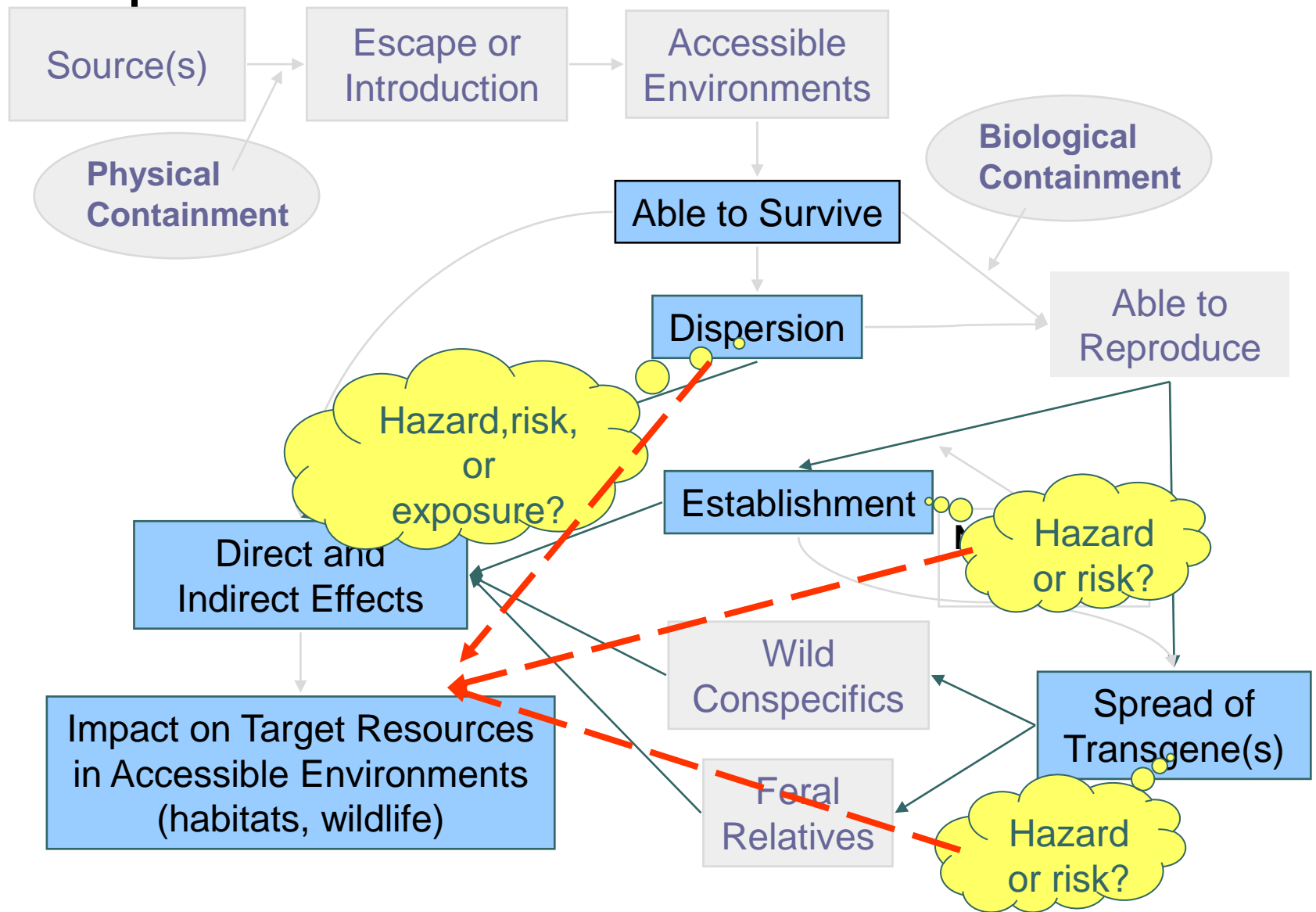
Consideration of the following factors:

1. Ability of GE animal to disperse into diverse communities upon release or escape
2. “Fitness” of GE animal within the receiving ecosystem
3. Stability and resiliency of the receiving community

Conceptual Model for Hazard Characterization/Risk Assessment

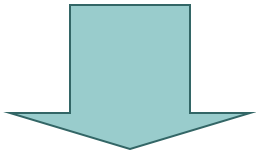


Conceptual Model for Hazard Characterization/Risk Assessment



Direct and Indirect Effects

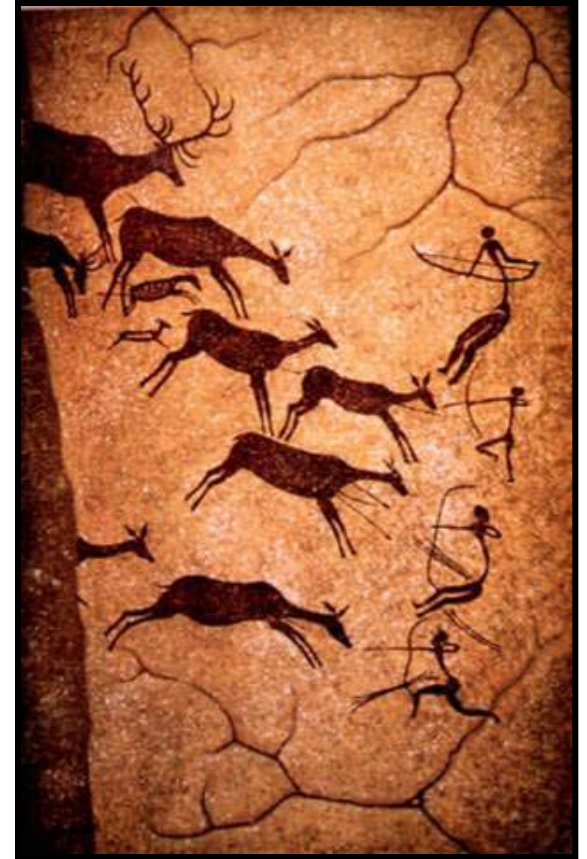
- Pathogen / disease transfer
- Genetic disturbance
- Resource competition
- Displacement
- Habitat destruction
- Predation



Population changes



Community/Ecosystem disruptions





Inter-Agency Coordination

- Yes!
- Some interactions legislated
 - NEPA
 - FDAAA
 - Endangered Species Act
 - Lacey Act
- Staff level interactions ongoing
- OSTP interagency biotech working group

Take Home Message

- No environmental evaluations yet done for intentional environmental releases
 - Likely to be an involved process
 - Very data intensive
 - Require good risk assessment models and endpoints
- Agency is open to input from stakeholders
 - Come see us
- If developing an animal for intentional release
 - Come see us early to expedite the process
 - Help us ask the right risk questions
 - Ensure adequate data generated



● ● ● | **Thanks!**

Contact info:

Eric Silberhorn

Eric.Silberhorn@fda.hhs.gov

240 276-8224

Larisa Rudenko

Larisa.Rudenko@fda.hhs.gov

240 276-8245

