



BIO GUIDANCE

ON

GENETICALLY ENGINEERED ANIMAL

STEWARDSHIP

DISCLAIMER

This Animal Stewardship Guidance document (Guide) is solely an educational tool and guidance document to assist a product developer (user) in the development and application of a stewardship program related to the technology of genetically engineered (GE) animals. The guidance is flexible and its application will differ according to the size, nature and complexity of the organization, animals and animal products involved. The guidance is representative and not exhaustive.

It is the responsibility of any user of this document to consider that user's specific circumstances when: 1) developing a stewardship program specific to its business, and 2) in implementing the stewardship program and meeting any applicable legal requirements. This Guide is not, and should not be used as, a substitute for: a user's own individual understanding of its legal requirements; consultation by a user with legal counsel; or direct contact with the appropriate regulatory agency (ies). Legal requirements may be issued or revised by government agencies after the publication date of this Guide.

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BIO Guidance on Genetically Engineered Animal Stewardship

Executive Summary

This Guidance on Genetically Engineered Animal Stewardship (“Guidance” or “BIO Guidance”) is being developed by BIO’s Animal Policy Committee (APC) to address the stewardship of genetically engineered (GE) animals. This Guidance is ultimately targeted toward providing stewardship throughout the full animal and (or) animal product life cycle. This Guidance will assist companies and the industry in developing and adopting stewardship principles for conducting research, and developing and commercializing safe and efficacious agricultural and biomedical products from GE animals for societal benefit. The first guideline developed for this Guidance is related to research and development, and is a strong step forward to help support this innovative technology in an emerging marketplace for animals and animal products.

Mission of BIO’s APC Stewardship Initiative

The mission of BIO’s APC Stewardship Initiative is to institute and promote guidelines for the development and use of GE animals, which promote good animal welfare, enhance industry credibility, and comply with current regulatory requirements.

Background and Introduction

The focus of this Guidance is to support the responsible development and use of GE agricultural animals for agricultural, biomedical, and industrial applications. The genetic engineering of livestock, including poultry and fish, has the potential to improve public health, food nutrition and safety, enhance animal welfare and minimize the impact of animal agriculture on the environment. For the purpose of this Guidance the focus is on vertebrate members of the animal kingdom that are agricultural animals.

This Guidance places a high priority on the industry’s stewardship of animal well being. The industry involved with production of GE animals, until recently, has been centered primarily in North America, with the United States having the most developed regulatory system of government oversight. So references to government oversight in this Guidance will focus on the United States.

For over two decades, product developers in the biotechnology industry have been conducting research and development while following strict governmental standards for good animal welfare in the development of GE animals and their products. In addition to animal well being, animal product safety and efficacy are critical elements to the stewardship of animal biotechnology.

To reach these stewardship goals, BIO supports an appropriate regulatory framework, which includes a rigorous mandatory regulatory process that is coordinated among relevant governmental agencies for GE animals and their products. For example, in the United States,

coordination is expected among the agencies involved in approving GE animals and products derived from them, primarily, the Food and Drug Administration (FDA) and the U.S. Department of Agriculture (USDA), as well as among individual components within the relevant agencies. The U. S. industry seeks timely approvals of the animals and their products - an approval affirming the government's finding of safety and effectiveness. A final guidance document explaining FDA's regulation of GE animals was published in 2009, and the USDA has requested information from the public regarding its role in regulating these animals and their products. While FDA recently clarified the regulatory process for GE animals containing heritable recombinant DNA constructs, the FDA signaled their intention to provide additional guidance for GE animals with non-heritable constructs. Therefore, this BIO Guidance covers GE animals containing either heritable or non-heritable recombinant DNA constructs.

Purpose

This Guidance will provide information for the development and implementation of stewardship programs for product developers that plan to engage in research, development and commercialization of GE animals. The Guidance is being developed as a series of educational modules that can be adapted to the specific activities pertinent to the user's own operations. The modules that are planned for inclusion in the Guidance include **Research and Development, Commercialization, Post-Market Monitoring, and Discontinuation -Product Recall**. Each module will provide guidelines under the following six themes: 1) **Animal Identification, Labeling, and Inventory Control**; 2) **Animal Well Being**; 3) **Product Safety**; 4) **Animal Health**; 5) **Environment**; and 6) **Worker Safety**. The guidelines for the first module, Research and Development, are provided below.

The guidelines in the first module are intended to be flexible and will differ in their application according to the animal species, the animal products, and the size, nature and complexity of the industry or other organizations that are product developers. The guidelines in the first module are focused primarily on North America.

International guidelines for GE animals either have not been initiated or are in various stages of development. It is intended that in the future, the BIO guidelines will assist developers throughout the world in developing and adopting stewardship principles for conducting research, and developing and commercializing agricultural and biomedical products from GE animals. Further development of stewardship programs for GE animals will be facilitated by aligning the regulatory processes for GE animals throughout the world.

Scope

This Guidance addresses stewardship of GE animals through the life cycle of animals and animal products, addressing engineered-derived traits that could be present in the environment, food, feed, or products for human health, industrial, or consumer applications. It is being designed to provide guidelines for each stage of the animal and animal product lifecycles, from initial research and development through commercialization, post-market monitoring and discontinuation and (or) product recall activities.

Acronyms

AAALAC International Association for Assessment and Accreditation of Laboratory Animal Care International

AWA Animal Welfare Act

BIO Biotechnology Industry Organization

CCAC Canadian Council on Animal Care

DNA Deoxyribonucleic acid

EPA U.S. Environmental Protection Agency

FASS Federation of Animal Science Societies

FDA U.S. Food and Drug Administration

FDA, CBER FDA, Center for Biologics Evaluation and Research

FDA, CDRH FDA, Center for Devices and Radiological Health

FDA, CVM FDA, Center for Veterinary Medicine

FFDCA U. S. Federal Food Drug and Cosmetic Act

GE Genetically Engineered

IACUC Institutional Animal Care and Use Committee

NIH U.S. National Institutes of Health

NIH, OBA NIH, Office of Biotechnology Activities

NIH, OLAW NIH, Office of Laboratory Animal Welfare

OIE World Organization for Animal Health

OSHA Occupational Safety and Health Administration

PHS Policy Public Health Service Policy on Humane Care and use of Laboratory Animals

PHS U.S. Public Health Service

rDNA Recombinant deoxyribonucleic acid

SOP Standard Operating Procedure

USDA U.S. Department of Agriculture

USDA, APHIS USDA, Animal and Plant Health Inspection Service

USDA, APHIS, BRS USDA, APHIS, Biotechnology Regulatory Services

Definitions

The following definitions are being used for the purpose of this Guidance.

Agricultural animal: Animals whose products have historically been intended to be consumed as food or worn as clothing.

Animal: Any member of the animal kingdom Animalia except a human. Various statutes and guidelines have different definitions of “animal”.

Animal product: Any product derived from an animal.

Animal health: The state or condition of an animal as related to disease and physiological normalcy.

Animal welfare: The state or condition of an animal regarding the animal’s attempts to cope with its environment. Good animal welfare requires application of veterinary preventive and clinical medicine, appropriate shelter, management, nutrition, humane handling, and humane killing (euthanasia) when necessary. Ensuring good animal welfare includes consideration for all aspects of animal well being.

Animal well being: A state or condition of an animal, physically and psychologically, which advocates good behavior patterns, pathological and immunological traits, physiological and biochemical characteristics, and reproductive and productive performance of the individual animal.

Biosafety: Measures to reduce the risk of unintended transmission and accidental release of genetic material via preventative measures related to containment and confinement of animals.

Biosecurity: Measures to reduce the risk of movement of important biological materials, including by theft or intentional release, via preventative measures over and above animal biosafety precautions, for example, as with pathogenic organisms.

Biotechnology: The application of recombinant DNA technology or genetic engineering. Sometimes referred to as any technological application that uses biological systems (including cells and biological molecules), living organisms, or derivatives thereof to make or modify products or processes for specific uses.

Commercialization: The sale of products to the public (following government pre-market approval).

Confinement: Biological or physical measures to restrict movement and the reproductive capability of animals.

Construct: Functional unit necessary for the transfer or the expression of a gene of interest. Generally refers to a specific DNA sequence.

Containment: Physical measures to restrict the movement of biological samples or animals.

Environment: The air, water, soil, plants, wildlife, their interaction with each other, and other ecological systems external to investigational animals.

Genetic engineering: The direct manipulation of an organism's genes, including heritable and non-heritable recombinant DNA constructs. Genetic engineering is different from traditional breeding, where the organism's genes are manipulated indirectly. Genetic engineering uses the techniques of molecular cloning and transformation (uptake and expression of recombinant DNA constructs) to alter the structure and characteristics of genes directly.

Inventory system: A standard operational approach to record the identification and status of biological samples, animals, or other applicable entities in the production of genetically engineered animals.

Investigational animal: Any experimental animal in research and development including controls, sentinels that are housed with GE animals, GE animals, no-takes, non-transgenic surrogate dams and the progeny of GE animals (which in the United States are considered as GE animals, and not some derivative of the original GE animals).

Labeling: All labels and other written, printed, or graphic materials placed upon or accompanying any biological samples, animals, or products of GE animals. A description of the nature, properties, and conditions of use as well as potential adverse effects for a regulated product. A label may include descriptions of specific properties and changes for GE animals or for products derived from GE animals. For example, it may describe how to manage or maintain specific lines of GE animals in order to obtain the benefits derived from the genetic engineering. Labeling must not be false or misleading.

Livestock: Animals generally but not exclusively raised for food.

No-take: An animal that is derived from an embryo or cell line where direct genetic engineering (such as injection of construct cassettes) was attempted but apparently failed (transgene is not incorporated into the genome and therefore the animal is untransformed and does not express the trait of a transgene). Definition does not include non-transgenic surrogate dams, controls, sentinels, or progeny that did not inherit the recombinant DNA.

Product safety: Safety of a GE animal or a product from a GE animal in terms of safety to humans, to the animals themselves, or to the environment of any product, including in this context, a GE animal.

Product developer: Any person, organization, or institution, private or public that is seeking approval for commercialization of a product from a GE animal. Under FDA’s regulations a product developer is sometimes referred to as a “sponsor”.

Sentinel: A non-genetically engineered animal, usually closely genetically related, that lives with or around the GE herd that is monitored for disease coming in or spreading among the transgenic herd.

Stewardship: As it related to the genetic engineering of animals, stewardship is the initiative and processes undertaken by product developers to increase their control over and responsibility for the conduct of practices that promote good animal welfare, enhance industry credibility, and complement current regulatory requirements.

Surrogate dams: Female animals into which an embryo is transferred, and to which they are not genetically related, in order to carry a viable fetus through pregnancy and to parturition.

Tracking: Ability to trace or preserve the identity of an animal or products from an animal through final disposition.

Worker safety: Safety of personnel that are involved in any aspect of the production of a GE animal.

Format of the Guidance

An organization or product developer may be involved in one or more activities associated with the research, development, or ultimate commercialization of a GE animal or its products. To accommodate these different business models, this Guidance is being prepared as separate but coordinated modules of guidelines.

MODULE ONE -- Guidelines for Research and Development

The first stages in the development of a GE animal take place in a contained laboratory and (or) in an isolated animal facility that may range from an environmentally-controlled facility to an open-air facility similar to commercial animal production facilities. Given this range of facilities, product developers should anticipate having interaction with a variety of government entities, each operating under different statutory authorities, and with different, but sometimes overlapping responsibilities.

The government's laws and regulations applicable to working with r-DNA molecules, microorganisms and investigational animals can be incorporated into standard operating procedures (SOPs) for animal facilities and for research operations at those facilities. Product developers should follow these laws and the relevant government recommendations (i.e., "guidance documents") in order to promote consistency and predictability in the regulatory process. Some of the pertinent laws and regulations are described in these BIO Guidelines for Research and Development (R&D Guidelines), but there may be others that are applicable to product developers in different jurisdictions. However, these R&D Guidelines are not intended to provide product developers with legal advice or an authoritative analysis of the relevant laws, regulations, or government policies

The R&D Guidelines that follow address six themes: 1) Animal Identification, Labeling, and Inventory Control; 2) Animal Well Being; 3) Product Safety; 4) Animal Health; 5) Environment; and 6) Worker Safety.

Theme 1) Animal Identification, Labeling and Inventory Control

Product developers are required to comply with the applicable requirements of relevant governmental agencies regarding the identification, labeling, and disposition of investigational GE animals.

- FDA regulations concerning investigational use of new animal drugs are codified at Section 511.1 in Title 21 of the Code of Federal Regulations. In 2009, FDA clarified its approach to regulate rDNA constructs in GE animals under the new animal drug provisions of the Federal Food, Drug, and Cosmetic Act in Guidance 187: Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Products ("FDA Guidance" or "Guidance 187") which is found at <http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM113903.pdf> .
Prior to approval, the Investigational New Animal Drug (INAD) regulations apply to investigational GE animals. These regulations specify requirements for labeling and record-keeping, animal disposition, and conditions under which food from animals used for clinical investigations can be introduced into the food supply.
 - Section 511.1(b) requires that prior to shipping a new animal drug for clinical tests; a product developer is required to submit a Notice of Claimed Investigational Exemption for a New Animal Drug (INAD Notice) containing

specified information. In Guidance 187, FDA recommends that developers open an INAD file as early as possible in order to promote cooperative discussions regarding the data necessary to support the ultimate commercialization of a GE animal and/or products derived from it.

- FDA also recommends that sponsors contact FDA to determine the appropriate labeling that should accompany the particular investigational GE animal or its products. The 2009 FDA Guidance addresses the type of information that may be required for labeling investigational GE animals, based on labeling required for New Animal Drugs: “In the context of GE animals, [labeling to be used for the NADA] includes labels and other written, printed information (i.e., labeling) that will accompany the GE animals. Labeling should include a summary description of the article, the animal into which the article is introduced (e.g., common name/breed/line; genus and species), the name of the resulting GE animal line, and the intended use of the GE animal containing the article. Where the labeling for a GE animal contains animal care or safety information (e.g., husbandry or containment), we recommend that the labeling accompany the animal throughout all stages of its lifecycle.” Note: For this section, the term “article” refers to the regulated article and is the rDNA construct in a GE animal that is intended to affect the structure or function of the body of the GE animal, according to the Federal Food, Drug, and Cosmetic Act (FFDCA) definition of a new animal drug.

- According to the 2009 FDA Guidance, a “primary goal during the investigational phase of development of the GE animal is to ensure that edible products from the GE animals do not enter the food or feed supply without prior FDA authorization. Edible products include, but are not limited to milk, honey, eggs, muscle tissue, as well as other tissues such as liver, kidney, skin, and fat.” Specifically, a product developer is required to obtain FDA authorization before the products of any investigational animal (such as no-takes or surrogates) may enter the food or feed supply. 21 CFR § 511.1(b)(5). For those animals subject to slaughter inspection by the USDA Food Safety and Inspection Service (FSIS), FDA will inform FSIS if FDA safety concerns have been met and whether FDA has granted the developer an Investigational Food Use Authorization. Failure to obtain an Investigational Food Use Authorization will render any such food products adulterated under the FFDCA.

- In addition, when the investigational animals or products derived from them are shipped to other investigators, the 2009 FDA Guidance notes that, under the INAD regulations, “All shipments must bear labeling that clearly identifies that edible products derived from investigational animals are not to be used for food without prior authorization from FDA.”

- In order to facilitate the disposition of investigational animals, the 2009 FDA Guidance recommends that product developers establish an inventory and

tracking system to uniquely identify each animal, related products, and samples. The 2009 FDA Guidance also encourages the development of a disposition plan for all classes of investigational animals and animal products. FDA recommends “that all surplus investigational animals and their biological products be disposed of by incineration, burial, or composting, and that appropriate records be kept of animal identification and disposition.” The guidance also notes that alternative disposition may be appropriate in some special cases, provided that FDA safety concerns are met. Care should be given to use proper euthanasia techniques under veterinary supervision.

- Finally, the INAD regulations require a product developer maintain adequate records on each shipment of an investigational animal containing an investigational new animal drug (the rDNA construct). 21 CFR § 511.1(b)(3). Moreover, a product developer is required to have each investigator in the study create complete records of the investigation (including records of receipt and disposition of the investigational animal) and furnish timely reports regarding the investigation to the product developer. 21 CFR § 511.1(b)(7). All product developer and investigator records are required to be maintained for two years after the termination of the investigation or approval of the New Animal Drug Application, or longer, as may be required by other regulatory authorities.
- Product developers that receive federal government research funding from the National Institutes of Health (NIH) are required by condition of the research grant to comply with the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines). The NIH Guidelines provide specific identification and disposal guidance on animals larger than laboratory animals including cattle, swine, sheep, goats, horses, and poultry in Appendix Q (entitled “Physical and Biological Containment for Recombinant DNA Research Involving Animals”).
 - Regarding the ability to identify investigational GE animals, the NIH Guidelines state: “All genetically engineered neonates shall be permanently marked within 72 hours after birth, if their size permits. If their size does not permit marking, their containers should be marked. In addition, transgenic animals should contain distinct and biochemically assayable DNA sequences that allow identification of a transgenic animal from among non-transgenic animals.”
 - Regarding animal disposition, the NIH Guidelines indicate that the carcass of an animal covered by Appendix Q and containing rDNA or an rDNA-derived organism is to be “disposed of to avoid its use as food for human beings or animals unless food use is specifically authorized by an appropriate Federal agency.” In addition, the NIH Guidelines state that a “permanent record shall be maintained of the experimental use and disposal of each animal or groups of animals.”

Theme 2) Animal Well Being

Product developers of GE animal technology are required to comply with governmental statutes and regulations pertaining to use of animals in research and development. Individual product developers should be familiar with the requirements of any relevant government entity and whether those requirements apply to their research activities.

- In the United States, product developers are required to comply with the applicable provisions of the federal statute and regulations designed to protect animal well being. These include provisions of the Animal Welfare Act (AWA) found at http://www.aphis.usda.gov/animal_welfare/downloads/awa/awa.pdf and the AWA regulations codified in 9 CFR Subchapter A, found at http://www.aphis.usda.gov/animal_welfare/downloads/awr/awr.doc. The AWA defines “animal” as:

“any live or dead dog, cat, monkey (nonhuman primate mammal), guinea pig, hamster, rabbit, or such other warm-blooded animal, . . . [which] is being used, or is intended for use, for research, testing, experimentation, or exhibition purposes, or as a pet; but such term excludes (1) birds, rats of the genus *Rattus*, and mice of the genus *Mus*, bred for use in research; (2) horses not used for research purposes; and (3) other farm animals, such as, but not limited to, livestock or poultry used or intended for use as food or fiber, or livestock or poultry used or intended for use for improving animal nutrition, breeding, management, or production efficiency, or for improving the quality of food or fiber. With respect to a dog, the term means all dogs, including those used for hunting, security, or breeding purposes.” 7 USC § 2132(g). Developers using farm animals should be advised to contact the appropriate USDA, APHIS, Animal Care (AC) Regional Office found at http://www.aphis.usda.gov/animal_welfare/downloads/acorg.html, to determine whether their project is regulated under the AWA.

- Under the AWA, product developers are required to register with the USDA when conducting research with animals. 9 CFR § 2.30. USDA, APHIS’s AC Policy 10 states that a facility that produces GE animals is using such animals in research, tests or experiments to determine the effect of the unconventional introduction of synthetic, species-foreign, or other such genetic material on the phenotype of the animal. APHIS AC has specifically stated its intention to regulate facilities conducting genetic engineering that results in a live (whole) animal species to be covered by the AWA

as a research facility under the AWA. As such, product developers are required to be registered with USDA, meet AWA requirements, submit to unannounced site inspections, and have Institutional Animal Care and Use Committees to oversee and approve their protocols. The policy is available at http://www.aphis.usda.gov/animal_welfare/policy.shtml.

- Under the AWA, product developers in the United States are required to establish an Institutional Animal Care and Use Committee, a description of which is provided at [9 CFR § 2.31](#).
- In the United States, product developers that receive funding for research from the Public Health Service (PHS) are required to comply with the PHS Policy on Humane Care and Use of Laboratory Animals and the *Guide for the Care and Use of Laboratory Animals*. The Policy can be found at <http://grants.nih.gov/grants/olaw/references/phspol.htm#AnimalWelfareAssurance>. The Guide can be found at http://www.nap.edu/catalog.php?record_id=5140.

Under the PHS Policy, an animal is “any live, vertebrate animal used or intended for use in research, research training, experimentation, or biological testing or for related purposes.”

- Product developers that receive PHS funding, and that use live vertebrate animals in research, testing or training, are required to comply with the PHS Policy and, when requested by the NIH Office of Laboratory Animal Welfare (OLAW), are required to prepare a document known as “Animal Welfare Assurance,” which is then approved by the NIH, OLAW. This requirement is contained in the “Public Health Service Policy on Humane Care and use of Laboratory Animals.” The Policy can be found at <http://grants.nih.gov/grants/olaw/references/phspol.htm#AnimalWelfareAssurance>.
- Product developers, in complying with the PHS Policy, must register with the National Institutes of Health (NIH) for animal care and the review of the animal facilities.
- The PHS Policy on Humane Care and Use of Laboratory Animals also requires compliance with the AWA and its regulations. In addition, the NIH Guidelines require compliance with the AWA’s animal welfare standards. *See*, for example, NIH Guidelines, Appendix Q. The NIH Guidelines can be found at http://oba.od.nih.gov/oba/rac/guidelines_02/NIH_Guidelines_Apr_02.htm.
- In the United States, the FDA requires compliance with the AWA and its regulations as noted in "Points to Consider" (1995) by FDA’s Center for Biologics Evaluation and

Research (CBER) and found at

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/UCM153306.pdf> . As stated above, animal well being in research and development is regulated under the law. Legal requirements vary depending on the animal species and the research purpose. Product developers of GE animals are required to comply with the law, and when the law does not address a specific species or research purpose, these R&D Guidelines encourage product developers to meet the spirit of the law as appropriate to the species or the purpose. To this end, and regardless of the animal species or research purpose, [product developers should take the following](#) steps to meet the appropriate animal well being goals:

- Have a licensed attending veterinarian either on the product developer's staff or under contract, to oversee animal welfare and care.
- Establish an oversight committee responsible for animal care and use in research.
 - For example, as noted above under the AWA, product developers in the United States are required to establish an Institutional Animal Care and Use Committee, a description of which is provided at [9 CFR § 2.31](#) .
- Register with the appropriate governmental agencies responsible for animal care and the review of animal facilities.
 - For example, in the United States, product developers that receive funding for research, testing or training using live vertebrate animals from the PHS must comply with the provisions of the PHS Policy and, when requested by the NIH OLAW, must prepare a document known as "Animal Welfare Assurance," which is then approved by the NIH, OLAW. This requirement is contained in the "Public Health Service Policy on Humane Care and use of Laboratory Animals." The Policy can be found at <http://grants.nih.gov/grants/olaw/references/phspol.htm#AnimalWelfareAssurance>.
 - As another example under the AWA, product developers are required to register with the USDA when conducting research with animals. 9 CFR § 2.30.
- Comply with any appropriate third party guidance that is endorsed by governmental agencies.
 - For example, in the United States, a facility may not need to be registered with the USDA or receive funding from NIH in order to warrant compliance with the agencies' regulations or guidance. Therefore, compliance with the AWA regulations and(or) the PHS Policy on Humane

Care and Use of Laboratory Animals and the *Guide for the Care and Use of Laboratory Animals* may be appropriate and enhance credibility.

- For example, in the United States, the USDA advises product developers that the recommendations of the *Guide for the Care and Use of Agricultural Animals in Research and Teaching* of the Federation of Animal Science Societies may be used as guidance on how to meet the already existing standards in the AWA regulations. The USDA policy articulating this position is found at http://www.aphis.usda.gov/animal_welfare/downloads/policy/policy29.pdf.
 - The Ag Guide may be found (currently under revision and open for public comment) at http://www.fass.org/agguide_review.asp.
 - As another example, in Canada, product developers should follow the recommendations of the Canadian Council on Animal Care.
- Accreditation by an independent third-party organization enhances compliance and credibility for a product developer. Therefore, product developers should consider becoming accredited by a third-party organization such as AAALAC International (www.aaalac.org) or another widely recognized professional organization.
 - Advances in animal stewardship are continually improving. Therefore, product developers should keep abreast of developments in international guidelines for animal welfare in biotechnology research. For example, the OIE, also known as the World Organization for Animal Health (www.oie.int), is active in the development of international standards for animal health and guidance for animal well being.

Theme 3) Product Safety

During the research and development phase, product developers should consider what governmental safety standards will apply to their GE animals and any products derived from those animals, with the goal of collecting data on the investigational animals that will support the ultimate animal and product's approval. Product developers should be aware of and comply with the requirements of relevant governmental authorities.

- In the United States, during the R&D phase, product developers may be subject to the FDA's Investigational New Animal Drug (INAD) requirements. The 2009 FDA Guidance provides advice and direction regarding the INAD process.
- The U.S. regulatory process for the development of a GE animal or its product begins when a product developer contacts the appropriate regulatory agency. The first agency to contact may be the FDA or more specifically, the Center for Veterinary Medicine (CVM) at FDA. Other agencies or centers within FDA may need to be contacted

subsequently, depending on the characterization of any product intended to be derived from the GE animal, e.g. CBER and/or CDRH. The 2009 FDA Guidance encourages developers “to contact CVM’s Animal Biotechnology Staff if you have questions about submitting a request to establish an INAD file... We recommend that you schedule a meeting with us (either in-person or via teleconference) soon after an INAD file has been established.”

- The 2009 FDA Guidance states “INAD requirements in 21 CFR 511.1(b) apply to investigational GE animals. ... In most cases, you will need to submit an INAD Notice prior to shipping any GE animals, but we strongly recommend that you submit an INAD Notice early in your development of GE animals. ... Also if you wish to introduce any food derived from investigational animals into the food or feed supply, you would need to get prior FDA authorization to do so through the INAD process. 21 CFR 511.1(b)(5).” Product developers should consult with their legal counsel and (or) FDA to determine the best time to request to establish an INAD file.
 - The act of creating an INAD file, and the INAD files themselves, are protected as confidential under the law, but a product developer may voluntarily disclose information to the public.
- As another example, in Canada, the product developer will need to contact Health Canada and the Canadian Food Inspection Agency (CFIA).
 - Health Canada considers novel foods, including animals produced through genetic engineering, to be subject to the regulations in Division 28, Part B, of the Food and Drug Regulations under the Food and Drugs Act. Therefore, developers producing animals through genetic engineering are required to comply with the applicable laws, which mean not introducing the products or by-products of these animals or their progeny into the human food supply in Canada, unless they have been subject to a pre-market safety assessment, which is required for novel foods.
 - The CFIA also considers novel feeds, including ingredients from animals produced through genetic engineering, to be subject to assessment before any derived products and by-products can be released in the feed chain.
 - Based on its guidelines for preparing a New Animal Drug Application (NADA), the 2009 FDA Guidance provides advice on acceptable scientific practices for using, verifying, and tracking the rDNA construct during the development process. This information is important to the demonstration of product safety needed in order to obtain FDA approval, and to assist the product developer in moving toward commercialization of the GE animal or its product. NAD regulations include Good Laboratory Practices (GLP) and the 2009 FDA Guidance document clarifies that these GLP’s apply to GE and investigational animals. The rules provided by FDA on

GLP are found at 21 CFR 58. For example, among other steps, product developers should:

- Establish SOPs for all processes used in development of GE animals for regulatory approval.
 - Establish and implement a system for identifying and labeling constructs in such a way that the information is retrievable. Data such as whether the construct or its expression product causes any toxicity are also important to collect during the R&D phase. Disposition should also be included as part of a comprehensive inventory system.
 - Maintain and retain documentation of construct identity and trace back that is secure, accessible, and retrievable. Data such as whether the construct contains any potentially mobilizable sequences are also important to collect during the R&D stage.
 - Product developers should establish and implement internal work processes and SOP's for detection of the rDNA constructs.
- The introduction of the rDNA construct into the host animal genome and its durability in subsequent generations is also addressed in the 2009 FDA Guidance. Again, acceptable scientific practices should be used, verified, and tracked in anticipation of seeking marketing approval for new products through robust, data-extensive applications. For example, among other recommendations, the 2009 FDA Guidance recommends that product developers establish and implement a system for identifying and labeling GE animals that will facilitate the collection of data on genotypic and phenotypic durability over multiple generations. In addition, the 2009 FDA Guidance indicates that information regarding the methodology used for construct introduction and the breeding strategy will be necessary for a complete New Animal Drug Application.
 - Regarding submitting data and other information required for product approval, the 2009 FDA Guidance recommends that product developers work with CVM to determine “the most efficient manner to submit all the . . . relevant information.”
- During the R&D phase, and with respect to the introduction of the rDNA construct into the host genome, product developers should:
 - Maintain and retain documentation of identity and trace back that is secure and accessible.
 - Establish and implement:
 - Labeling, tracking, and disposition as part of an inventory system; and
 - Procedures so that labels used to identify host material and GE animals are recorded and information pertinent to identity is retrievable.

- Establish and implement internal work processes and SOPs for detection of successful insertion events.
- Internationally, product developers should be familiar with, and apply appropriately the 2008 Codex guidelines for rDNA animals for food safety assessment. Those guidelines, referenced under the Codex Alimentarius, are found at www.codexalimentarius.net. As other international guidelines are developed for the safety of products from biotechnology-derived animals, product developers should stay abreast of these developments and apply the guidelines, as appropriate, depending on the species and/or research purpose.

Theme 4) Animal Health

Product developers are required to comply with the relevant federal and state statutes and regulations pertaining to animal health to prevent disease transmission. For example, in the United States, USDA, APHIS administers the Animal Health Protection Act (AHPA), and some states have corresponding statutes.

- Product developers should meet appropriate animal health goals for the individual animal and the herd by having a licensed attending veterinarian either on the product developer's staff or under contract, to oversee animal care and the maintenance of permanent animal health records.

In addition:

- In the 2009 FDA Guidance, FDA notes that various animal health guidelines that address physiologic, long-term effects on the animal and its longevity may be applicable to GE animals.
- U.S. PHS-funded research, testing and training must meet the standards in the PHS Policy as overseen by the NIH OLAW.
- Product developers that are using infectious agents as vectors or as test agents should comply with any relevant federal and state statutes and regulations pertaining to containment of such vectors, the animals or the test agents.
- Future regulatory requirements or guidance may be developed by state or federal agencies to address animal health issues as they arise. For example, USDA APHIS may develop guidance or regulations to complement and coordinate with FDA's regulatory process.
 - As another example, in Canada, the CFIA has expertise in animal health and has jurisdiction in this area under the Health of Animals Act.
- Product developers should comply, as applicable, with animal containment guidelines of relevant governmental agencies and other appropriate organizations (for example, CCAC or equivalent guidelines).

- Product developers should comply, as applicable, with biosecurity guidelines of relevant governmental agencies. For example, see Appendix Q of the NIH Guidelines.
- Techniques and procedures to promote and enhance animal health are continually improving. Therefore, product developers should keep abreast of developments in international guidelines for animal health in genetic engineering research. For example, the OIE, also known as the World Organization for Animal Health (www.oie.int), is active in the development of international standards for animal health.

Theme 5) Environment

Product developers are required to comply with the relevant federal and state statutes and regulations pertaining to containment and confinement practices of GE agricultural animals.

- Product developers should comply, as applicable, with requirements of state and local environmental protection regulations, including the handling of manure, bedding, wastewater, leftover feed, and animal disposal.
- The 2009 FDA Guidance notes that requirements for relevant environmental review and assessments (for example, under the National Environmental Policy Act (NEPA)) may be applicable to certain federal action regarding the development of GE animals.
 - For example, under NEPA, FDA’s “actions on INADs are considered federal actions, and as such may require preparation of an environmental assessment (EA) (21 CFR 511.1(b) (10), 21 CFR 25.15) or environmental impact statement (EIS) (21 CFR 25.22). Through the preparation of an EA or EIS, FDA will examine the potential for environmental impacts, including the potential for inadvertent release or escape of the GE animal and/or its products into the environment, and whether certain measures may mitigate any potential significant impacts that would adversely affect the human environment. Additionally, sponsors may be subject to applicable environmental requirements with respect to runoff from animal production facilities and land receiving animal waste under the Clean Water Act. 33 U.S.C. 1251 et. seq. and other statutes.”
 - For example, in the United States, regarding animal disposal, the 2009 FDA Guidance states “We encourage you to provide a disposition plan for all classes of investigational animals and animal products. We recommend that all surplus investigational animals and their biological products be disposed of by incineration, burial, or composting, and that appropriate records be kept of animal identification and disposition. In some special cases, alternative disposition may be appropriate provided that our safety concerns are met (see Section III.C) 21 CFR 511.1 (b) (5).”
- In Canada, the product developer may need to contact Environment Canada.

- Environment Canada is probably the first point of contact for product developers of GE animals if a developer wants to manufacture, import, or sell such an animal in Canada. Animals produced through genetic engineering and their progeny are considered to be "new substances" under the Canadian Environmental Protection Act 1999 and product developers are required to meet the Environment Canada notification requirements under the New Substances Notification Regulations.
- Product developers should comply with applicable containment and confinement guidelines of relevant governmental agencies and other appropriate organizations (for example, CCAC, FASS or equivalent organizations). In addition, product developers, as appropriate, also should meet the requirements of the NIH Guidelines, Appendix Q.
 - For example, product developers that receive federal government research funding from NIH are required to meet NIH requirements and establish an Institutional Biosafety Committee, which is required to be registered with NIH Office of Biotechnology Activities (OBA) (http://oba.od.nih.gov/rdna_ibc/ibc.html).
- Product developers should keep abreast of developments in international guidelines for environmental review and assessment in research on genetic engineering of animals. For example, the parties to the Cartagena Protocol on Biosafety (<http://www.cbd.int/biosafety/>) recently considered the evaluation of environmental risk assessment for GE animals, with a focus on fish.

Theme 6) Worker Safety

Product developers are required to comply with the relevant federal and state statutes and regulations pertaining to worker safety in the conduct of biotechnology research.

- Product developers should comply, as applicable, with established occupational health and safety programs consistent with federal, state, and local regulations depending on the facilities, research activities, and hazards involved.
- In the United States, product developers should comply, as applicable, with workplace requirements of the Occupational Safety and Health Administration (OSHA) and laboratory requirements for the NIH, Centers for Disease Control and Prevention, USDA, and Department of Homeland Security.
 - Such programs may include, for example, physical examinations; education; appropriate immunization schedules; access to first aid; physical protection; and maintenance of health records. The applicability of various requirements is generally determined based on work assignment. Laboratory requirements for conduct of molecular and genetic research (select agents, etc.) should be met, as appropriate, and all applicable biosecurity guidelines should be met. Worker protection containment issues should be met for safety of the personnel.

- For example, organizations that conduct animal activities in the U.S. PHS-funded research, testing and or training are required by the PHS Policy to have an occupational health and safety program consistent with the PHS policy.
- Personnel involved in undertaking research and development with GE animals should understand the relevant laws, regulatory requirements, and related guidance as provided by government regulatory agencies. This information should be incorporated, as appropriate, into an organization's stewardship program.
- Techniques and procedures to promote and enhance worker safety are continually improving. Therefore, product developers should keep abreast of opportunities to provide personnel with training in their respective job functions (for example: animal husbandry, animal care and handling, laboratory procedures); worker safety training for their respective job function; and worker certification programs with respect of laboratory procedures and animal care (for example: the American Association for Laboratory Animal Science, the American Registry of Professional Animal Scientists, the American Veterinary Medical Association and the International Embryo Transfer Society).

Guidance Resources for Research and Development

Regulatory and Other Guidance

Some examples of important information include the following:

AAALAC International. (www.aaalac.org)

American Association for Laboratory Animal Science. (<http://www.aalas.org/index.aspx>)

American Registry of Professional Animal Scientists. (<http://www.arpas.org/>)

Animal Health Protection Act. U.S. Code, Title 7, Chapter 109.
(http://www2.law.cornell.edu/uscode/uscode07/usc_sup_01_7_10_109.html)

Animal Welfare Act. U. S. Code, Title 7, Section 54.
(http://www.aphis.usda.gov/animal_welfare/downloads/awa/awa.pdf)

American Veterinary Medical Association. (<http://www.avma.org/>)

Canadian Council on Animal Care. 1997. CCAC Guidelines on Transgenic Animals.
(http://www.ccac.ca/en/CCAC_Programs/Guidelines_Policies/GDLINES/TRANSGEN/TRANS_GE1.HTM)

Canadian Environmental Protection Act. 1999. (1999, c.33).
(<http://laws.justice.gc.ca/en/showtdm/cs/C-15.31>)

Cartagena Protocol on Biosafety. (<http://www.cbd.int/biosafety/>)

Codex Alimentarius. 2008. Guideline for the Conduct of Food Safety Assessment of Foods Derived from rDNA Animals.
(http://www.codexalimentarius.net/download/standards/11023/CXG_068e.pdf)

Council on Environmental Quality. 2001. CEQ/ OSTP Assessment: Case Studies of Environmental Regulations for Biotechnology.
(http://www.ostp.gov/galleries/Issues/ceq_ostp_study1.pdf),
(http://www.ostp.gov/cs/issues/CEQ_OSTP_Environmental_Regulation.html)

Federation of Animal Science Societies. 1999. Guide for the Care and Use of Agricultural Animals in Agricultural Research and Teaching. (<http://www.fass.org/page.asp?pageID=216>)

Federation of Animal Science Societies. Last dated July 1, 2009 and undergoing revision. Guide for the Care and Use of Agricultural Animals in Research and Teaching.
(http://www.fass.org/agguide_review.asp)

Federal Food, Drug, and Cosmetic Act. U.S. Code, Title 21, Chapter 9.
(<http://www4.law.cornell.edu/uscode/21/ch9.html>)

Food and Drug Administration, Center for Biologics Research and Evaluation. 1995. Points to Consider in Manufacture and Testing of Therapeutic Products for Human Use Derived from Transgenic Animals.
(<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/UCM153306.pdf>)

Food and Drug Administration, Center for Veterinary Medicine. 2009. Guidance for Industry 187, Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs.
(<http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM113903.pdf>)

Food and Drug Regulations (C.R.C., c. 870) of the Food and Drugs Act.
(<http://laws.justice.gc.ca/en/showdoc/cr/C.R.C.-c.870///en?page=1>)

Health of Animals Act, S.C. 1990, c. 21. (<http://laws.justice.gc.ca/en/H-3.3>)

International Embryo Transfer Society. (<http://www.iets.org/>)

National Institutes of Health. 2002. NIH Guidelines for Research Involving Recombinant DNA Molecules. National Institutes of Health, Bethesda, MD,
(http://oba.od.nih.gov/oba/rac/guidelines_02/NIH_Guidelines_Apr_02.htm)

National Institutes of Health, Office of Biotechnology Activities.
(<http://oba.od.nih.gov/rdna/rdna.html>)

National Institutes of Health, Office of Laboratory Animal Welfare.
(<http://grants.nih.gov/grants/olaw/olaw.htm>)

National Institutes of Health, Office of Laboratory Animal Welfare, Animal Welfare Assurance.
(<http://grants.nih.gov/grants/olaw/sampledoc/assur.htm>)

New Substances Notification Regulations (Organisms) (SOR/2005-248).
(http://laws.justice.gc.ca/en/showdoc/cr/SOR-2005-248/bo-ga:s_1/en#anchorbo-ga:s_1)

Public Health Service Policy on Humane Care and use of Laboratory Animals.
(<http://grants.nih.gov/grants/olaw/references/phspol.htm>)

U. S. Department of Agriculture. 2008. Genetically Engineered Animals, Request for Information.
(<http://www.aphis.usda.gov/newsroom/content/2008/09/content/printable/FINAL%20docket%2006-188-1.pdf>)

U.S. Department of Agriculture. 2006. APHIS Animal Care Stakeholder Update on Revised Policies.
(http://www.aphis.usda.gov/animal_welfare/downloads/stakeholder/stakeholder5.pdf)

World Organization for Animal Health. (www.oie.int)

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