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Guidance for Industry

Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs

Final Guidance

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Additional copies of this guidance document may be requested from the Communications Staff, HFV-12, Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, and may be viewed on the Internet at http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm.

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Containing Heritable Recombinant DNA Constructs

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. Introduction and Background

Since its first demonstration as proof of principle by Cohen and Boyer in 1973, recombinant DNA (rDNA) technology has been applied to microorganisms, plants, and animals. Various agencies across the US government (USG) have provided guidance and regulations to affected stakeholders describing the regulation of these recombinant DNA (rDNA), or genetically engineered (GE), plants and microorganisms and of products produced by them. GE animals have been produced since the early 1980s when Brinster et al. (1982) and Palmiter et al. (1982) reported on the development of GE mice. Not long thereafter, Hammer et al. (1985) demonstrated that rabbits and pigs could also be genetically engineered. Now, more than two decades later, many different species, including those traditionally consumed as food, have been genetically engineered with various rDNA constructs.

For the purpose of this guidance, FDA defines "genetically engineered (GE) animals" as those animals modified by rDNA techniques, including the entire lineage of animals that contain the modification. The term GE animal can refer to both animals with heritable rDNA constructs and animals with non-heritable rDNA constructs (e.g., those modifications intended to be used as gene therapy). Although much of this guidance will be relevant to non-heritable rDNA constructs, and FDA intends to regulate non-heritable constructs in much the same way as described in this guidance for heritable constructs, this guidance only pertains to GE animals containing heritable rDNA constructs. We may issue a separate guidance on the regulation of GE animals bearing non-heritable constructs to discuss when those constructs would be under FDA jurisdiction and the kinds of information that would

be relevant for FDA's review. In this guidance, we will use the term "GE animal" to refer to GE animals with heritable rDNA constructs.

GE animals currently being developed can be divided into six broad classes based on the intended purpose of the genetic modification: (1) to enhance production or food quality traits (e.g., pigs with less environmentally deleterious wastes, faster growing fish); (2) to improve animal health (e.g., disease resistance); (3) to produce products intended for human therapeutic use (e.g., pharmaceutical products or tissues for transplantation; these GE animals are sometimes referred to as "biopharm" animals); (4) to enrich or enhance the animals' interactions with humans (e.g., hypo-allergenic pets); (5) to develop animal models for human diseases (e.g., pigs as models for cardiovascular diseases); and (6) to produce industrial or consumer products (e.g., fibers for multiple uses).

The Center for Veterinary Medicine ("CVM", "we", "us", "our") of the United States Food and Drug Administration (FDA or the agency) has been working on applications submitted by developers of GE animals under the New Animal Drug provisions of the Federal Food Drug and Cosmetic Act (FFDCA or the Act), 21 USC 321 et seq. This guidance is intended to clarify our requirements and recommendations for producers and developers ("sponsors," "you") of GE animals and their products. CVM will work closely with the other Centers at FDA that regulate pharmaceuticals or other medical products derived from biopharm animals to ensure that our oversight is complementary and not unnecessarily duplicative. Developers of GE animals should contact CVM early in the development of their GE animal; developers whose animals are already well under development also should contact CVM. We intend to issue additional guidance to describe more fully how various components of the New Animal Drug provisions of the Act apply to biopharm animals and how CVM will implement them, the division of responsibilities between CVM and the other Centers regarding biopharm animals and products derived from them, and, more generally, how CVM and the other Centers will work interactively to regulate biopharm animals and their products. Developers of GE animals should come to CVM early in the process.

In addition to this guidance, there are other guidelines and laws that may apply to GE animals:

- Existing guidances and other documents prepared by other FDA Centers including the Points to Consider in the Manufacture and Testing of Therapeutic Products for Human Use Derived from Transgenic Animals (1995) http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulator

yInformation/OtherRecommendationsforManufacturers/UCM153306.pdf, and Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Xenotransplantation/ucm092707.pdf.

- Federal laws, regulations, and guidelines for the humane care, handling, and slaughter of animals, as well as guidelines in place at your institution or establishment;
- Applicable federal, state, local and tribal laws, regulations, and guidelines addressing environmental safety, including those NIH guidelines that apply to your institution or establishment;
- Applicable federal, state, local and tribal laws, regulations, and guidelines pertaining to the importation, interstate movement, or release of wildlife;
- Federal laws, regulations, and guidelines governing the import or export of animals across US boundaries; and
- Other applicable federal, State, or local laws, regulations and guidelines.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word "should" in Agency guidances means that something is suggested or recommended, but not required.

II. Statutory and Regulatory Authority

A. The Regulated Article

FDA's authority over new animal drugs comes from the FFDCA (21 U.S.C. 321 et seq.). The definition of a drug, in section 201(g) of the Act, includes "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals;" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals." The definition of "new animal drug" in section 201(v) of the Act includes that it is a drug intended for use in animals that is not generally recognized as safe and effective for use under the conditions prescribed,

recommended, or suggested in the drug's labeling, and that has not been used to a material extent or for a material time.

Generally under the Act, a new animal drug is "deemed unsafe" unless FDA has approved a new animal drug application (NADA) for that particular use, unless the drug is only for investigational use and conforms to specified exemptions for such use under an Investigational New Animal Drug (INAD) exemption (21 USC 360b(a)(1), (a)(3)), or unless the drug is used in conformance with regulations promulgated under sections 512(a)(4) or (5) of the Act (21 U.S.C. 360b(a)(4) or (5)).

The rDNA construct in a GE animal that is intended to affect the structure or function of the body of the GE animal, regardless of the intended use of products that may be produced by the GE animal, meets the FFDCA drug definition. A non-heritable rDNA construct that is intended to affect the structure or function of a GE animal or to cure, mitigate, or treat a disease in the animal also meets the drug definition.[1] As noted previously, this guidance does not address such constructs, and it is our intent to issue an additional guidance to address the issues raised by GE animals containing non-heritable constructs.

In most cases, the methods used to introduce a new rDNA construct into the germline of an animal do not control the site in the genome where the construct will end up. Therefore, animals derived from different introductions of rDNA constructs (referred to as "transformation events") will likely have their rDNA constructs at different sites in the genome. The rDNA construct at a specific site in the genome is the subject of the NADA.

Because the site at which an rDNA construct is located can affect both the health of the animal and the level and control of expression of the construct (i.e., its effectiveness), in general, each animal lineage derived from a separate transformation event (or series of

[1] FDA does not intend to regulate rDNA constructs that meet the definition of a veterinary biologic and that are regulated by the Animal and Plant Health Inspection Service (APHIS) of the United States Department of Agriculture (USDA). 21 CFR 510.4. FDA intends to develop a memorandum of understanding with APHIS that will clarify the division of responsibilities between FDA and APHIS for GE animals carrying such rDNA constructs. We also recognize that EPA may assert jurisdiction over certain GE animals as well. In addition, FDA is discussing with other agencies the best approach for oversight of GE insects. Future guidance may be developed to address them. FDA also will work with other relevant federal and state agencies should it receive a request for investigation or approval of a GE wildlife animal ultimately intended for release into the wild.

transformation events) is considered to contain a separate new animal drug subject to a separate new animal drug approval. However, during the investigational phase, a single INAD file may be established containing information on investigational GE animals that contain different numbers or types of rDNA constructs, or rDNA constructs at different integrations sites, prior to selecting the GE animal intended for commercialization.

Each new animal drug approval covers all animals containing the same rDNA construct (the regulated article or new animal drug) derived from the same transformation event, including, for example, animals containing that rDNA construct as a result of breeding between a non-GE animal and a GE animal. We consider all GE animals derived from the same transformation event to contain the same article and to be subject to evaluation under a single NADA. As a short hand in this guidance document, we sometimes refer to regulation of the article in such GE animals as regulation of the GE animal.

Because GE animals that are being used for commercial purposes are likely to be descendents of the initial GE animal, rather than the initial GE animal itself, the NADA safety and effectiveness evaluations should be focused on a generation as close to those animals to be used for commercial purposes as possible. Sponsors will need to demonstrate that following approval and use in commerce, the construct and/or phenotype are stably maintained in a representative sample of animals. 21 CFR 514.1(b)(5).

B. Enforcement Discretion for INAD or NADA Requirements for Certain GE Animals

Although all GE animals are subject to premarket approval requirements, in certain circumstances, based on the risk(s) they pose, we intend to exercise enforcement discretion with regard to INAD and NADA requirements for certain GE animals (that is, in specified circumstances, we do not intend to enforce the INAD and NADA requirements, including those described in this guidance). For example, FDA has not and does not intend to take enforcement action with respect to INAD and NADA requirements for: (1) GE animals of non-food-species that are regulated by other government agencies or entities, such as GE insects being developed for plant pest control or animal health protection, and that are under APHIS oversight; and (2) GE animals of non-food-species that are raised and used in contained and controlled conditions such as GE laboratory animals used in research institutions. Although we generally intend to exercise enforcement discretion with regard to INAD and NADA

requirements for such animals, we retain the discretion to take enforcement action if we learn of safety concerns associated with them.

Based on evaluation of risk factors, we may exercise enforcement discretion over INAD and NADA requirements for additional kinds or uses of non-food-species GE animals, as we did after reviewing information about *Zebra danio* aquarium fish genetically engineered to fluoresce in the dark (GloFish) (http://www.fda.gov/bbs/topics/NEWS/2003/NEW00994.html and *Int'l Ctr. for Tech. Assessment v. Thompso*n, 421 F. Supp. 2d 1 (D.D.C. 2006)). When FDA intends to exercise enforcement discretion about specific GE animal lineages, it plans to post statements describing that intent on its website.

When FDA reviews and approves an INAD or NADA, it complies with the requirements of the National Environmental Policy Act (NEPA), including a review of environmental risks where required. When FDA exercises its enforcement discretion over the INAD or NADA requirements, no NEPA review would take place. As a result, environmental risks are among the factors we intend to consider in determining whether to exercise enforcement discretion. Among the environmental and other factors we intend to consider when determining whether to exercise enforcement discretion are:

- Whether there is anything about the article itself that poses a human, animal, or environmental risk. For example, does the construct contain sequences that can cause human or animal disease either intrinsically or by recombination?
- Whether, in the event of an environmental release, the GE animal poses any more of an environmental risk than its non-GE counterpart.
- Whether there are concerns over the disposition of GE animals that could pose human, animal, or environmental risks e.g., would disposal of large numbers of dead GE ferrets containing a construct that makes them resistant to rabies pose a particular risk?
- Whether there are any other safety questions that have not been adequately addressed by the sponsor.

You can contact CVM's Animal Biotechnology Staff for further information on whether your GE animal might warrant our exercising some form of enforcement discretion.

Although we may decide to exercise enforcement discretion with respect to regulatory requirements for certain GE animals after reviewing information about potential risks, this decision may be reevaluated if we become aware of any changes in the GE animals' risk profiles. Such reevaluation could lead us to conclude that the GE animals should be subject to FDA enforcement action until a full NADA has been approved.

III. Investigational Use of GE Animals

As noted earlier, under the Act, in general a new animal drug is "deemed unsafe" unless the FDA has approved an application for that particular use (21 USC 360b), unless it is for investigational use and is subject to an exemption from the approval requirement that conforms to FDA regulations or unless it is used consistent with regulations promulgated under sections 512(a)(4) and (5) of the Act. 21 USC 360b(a)(3), (4), (5), (j). Certain new animal drugs may qualify for either conditional approval or indexing under the minor use and minor species sections of the Act; a GE animal and its products, however, are specifically excluded from these provisions. 21 USC 360ccc(a)(3)(A) and 21 USC 360ccc-1(a)(2).

FDA regulations concerning investigational use of new animal drugs are codified at section 511.1 in Title 21 of the Code of Federal Regulations (21 CFR 511.1). These regulations cover shipments in interstate commerce of new animal drugs for tests *in vitro* and in laboratory research animals (21 CFR 511.1(a)) and for clinical investigation in animals (21 CFR 511.1(b)). The INAD requirements in 21 CFR 511.1(b) apply to investigational GE animals. Further, the development of GE animals constitutes clinical investigation because it involves studying the effectiveness of the drug in the target species and the effects of the rDNA construct, including those of its expression product(s), on the animal containing it.

In general, the INAD regulations specify labeling and record-keeping requirements, animal disposition, and conditions under which food from animals used for clinical investigations under section 511.1(b) can be introduced into the food supply. Section 511.1(b) also requires that prior to shipping a new animal drug for clinical tests, a sponsor must submit a Notice of Claimed Investigational Exemption for a New Animal Drug (INAD Notice) containing specified information.

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. We will then establish an INAD file that will enable you to begin discussions with us on how best to develop the data and information that will be needed for an NADA, and to provide such data and information to us for evaluation and comment. 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). We recommend that prior to making a request for such authorization, you schedule a teleconference or in-person meeting with us to determine which classes of investigational animals may be suitable for consideration for food use.

We encourage you to contact CVM's Animal Biotechnology Staff if you have questions about submitting a request to establish an INAD file. We recommend that when you request the establishment of an INAD file, you include information on the technology you used in developing the GE animal (e.g., the species of animal to be under study, the introduced gene(s), and the intention of the modification, including any gene product(s) that may be produced). In general, we recommend that the level of detail provided at these early interactions approximate that used for NIH or other grant applications. Once we have established an INAD file, we will assign it a unique identifier (which we refer to as a file number) that you should use for all subsequent communications with us. As previously stated, an INAD file can encompass animals derived from multiple transformation events, even though an NADA would generally only cover animals derived from a single transformation event.

We recommend that you schedule a meeting with us (either in-person or via teleconference) soon after an INAD file has been established. In that meeting, you can acquaint us with the nature of the GE animal under development and the intended use. We can then provide you with more specific information on the kinds of regulatory responsibilities you have under an INAD, and the nature of the regulatory decisions we can make during the investigational phase of research, including the following:

A. Shipping and Labeling Investigational Animals and their Products

During the investigational phase of the development of a GE animal, animals may need to be moved from the initial laboratory or barn to other locations within the sponsor's facilities, or to other investigators at the same facilities or off-site. If the investigational animals or products derived from them are shipped to other investigators, it is important to ensure that those individuals/entities receiving the investigational animals or their products use them only for research purposes. 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. 21 CFR 511.1(b)(1)-(5). We recommend that you contact us to determine the appropriate labeling for the particular investigational GE animal or its products.

B. Animal Disposition

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. 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).

C. Investigational Food Use Authorizations

If you wish to introduce investigational animals or animal products into the food or feed supply, you must request an Investigational Food Use Authorization (21 CFR 511.1(b)(5)). For those animals subject to slaughter inspection by the USDA Food Safety and Inspection Service (FSIS), we will inform FSIS if our safety concerns are met and we grant you an Investigational Food Use Authorization.

FSIS has oversight of most meat, poultry, and egg products, and enforces tolerances (maximum allowable amounts) set by FDA on new animal drug residues in such products. FDA and FSIS have enjoyed longstanding open communications during the drug approval process, and are discussing how to adapt and improve these existing procedures to fully accommodate the needs of both agencies in addressing GE animals intended to go into the food supply.

We recommend that prior to making a food-use authorization request, you schedule a teleconference or in-person meeting with us to determine which classes of investigational animals may be suitable for consideration for food use and the nature and extent of data you will need to provide for us to make that determination.

D. Environmental Considerations

Actions on INADs are considered federal actions under the National Environmental Policy Act (NEPA), 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.

In order to determine the nature and extent of the environmental risk issues that your investigational GE animals may pose, we recommend that you contact us early in the development of your GE animals so that we can determine the scope of this environmental assessment. These early discussions can help to focus your environmental assessment under the NADA component as well.

Categorical exclusion from the requirement to prepare an EA may be possible under 21 CFR §25.33(e) for investigational studies on certain GE animals, if you can provide sufficient information for us to conclude that extraordinary circumstances will not exist (21 CFR 25.21). This should include sufficient information on the GE animals and their containment to allow us to conclude that use and disposal of any investigational animals or their products would not have a significant impact on the environment. If you intend to claim a categorical exclusion for an NADA, we recommend that you contact us soon after establishing an INAD to discuss whether your NADA is eligible for a categorical exclusion, and if so, to determine the nature of the information that would allow us to determine if an extraordinary circumstance exists that would require an EA or EIS.

IV. FDA Approval of GE Animals

A. Overview

Other than for investigational uses, section 512(a)(1) of the Act (21 U.S.C. 360b(a)(1)) requires that a new animal drug be the subject of an approved new animal drug

application (NADA) based on a demonstration that it is safe and effective for its intended use.

When submitting an NADA, you should include the results of any investigations you conducted under an INAD. We will evaluate the NADA to determine whether you have demonstrated that the new animal drug is safe and effective for its intended use. To demonstrate effectiveness of an article intended to express an extractable protein (e.g., for use as a human biologic), generally you would simply have to show that the expression product is in fact expressed in the animal. To demonstrate effectiveness of an article intended to alter a characteristic of the resulting GE animal, in general you would have to show that the GE animal had the claimed altered characteristic (e.g., that its rate of growth was as claimed or that it was indeed resistant to a disease).

The agency is interested in increasing the transparency of its deliberations and actions. At present, we intend to hold public advisory committee meetings prior to approving any GE animal. We may revisit that policy in the future as we gain more experience with reviews of GE animals.

Additionally, as is the case for all NADAs, after completion of an NADA, the agency will post a summary of the information in the NADA file, including information used to assess safety (to the animal and for food or feed, if appropriate) and in support of the claims made by the sponsor. 21 CFR 514.11(e).

B. New Animal Drug Application Requirements

Section 512(b)(1) of the FFDCA describes the information that must be submitted to FDA as part of an NADA. These statutory requirements are further explained and expanded upon in the regulations for new animal drug applications, 21 CFR 514.1.

The application of some of the statutory and regulatory requirements for new animal drug applications to GE animals may not be obvious. For example, it may not be obvious how the requirement to provide a full list of the articles used as components of a drug as described in 512(b)(1)(B) of the FFDCA and 21 CFR 514.1(b)(4) of the NADA regulations applies to a GE animal. Therefore, this section of the guidance document provides a brief summary of the NADA requirements in 21 CFR 514.1 and describes how these requirements may be addressed for applications submitted for GE animals. Section IV.C describes our recommendations for how to present this information in the

structure of an NADA submission to meet these regulatory requirements and the statutory requirements of safety and effectiveness.

1. Identification (21 CFR 514.1(b)(1))

   Section 514.1(b)(1) requires that certain identifying information be provided including the nature of the application (i.e., original or supplemental application), the name and address of the applicant, date of application, and the trade and/or chemical name of the new animal drug.

   The information that should be provided to satisfy this requirement for a GE animal application is similar to that provided for a conventional new animal drug. In the case of a GE animal application, the "trade and/or chemical name of the new animal drug" should be described by identifying the animal, its ploidy and zygosity, the name and intended function of the rDNA construct, and the number and characterization of the insertion site(s)[2], as well as the intended use of the resulting GE animal. For a more complete description of how we recommend you present this information in the NADA submission, please see Section IV.C., Steps 1, 2, and 3.

   We consider this component to be critical to the structure and content of an NADA submission and so encourage you to consult with us on this topic as early as possible in the GE animal development process, for example, as an early part of the INAD process.

2. Table of Contents and Summary (21 CFR 514.1(b)(2))

   Section 514.1(b)(2) requires that an NADA include a table of contents which identifies the data and other material submitted, and a well-organized summary of information that (1) describes the chemistry of the new animal drug, and (2) describes the clinical purpose and provides a summary of laboratory and clinical studies.

   For more information on how we recommend you present this information in the NADA submission, please see Section IV.C., Steps 1, 2, and 3.

[2] The term "insertion site" in this document refers to the genomic location in the GE animal of the introduced rDNA construct, either chromosomally integrated or maintained as an extrachromosomal element. In general, we are most interested in characterizations that are performed in GE animals close to commercialization.

3. Labeling **(**21 CFR 514.1(b)(3))

   Section 514.1(b)(3) requires that an NADA include three copies of each piece of labeling to be used for the new animal drug.

   In the context of GE animals, this 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. We recommend that you contact CVM for further guidance regarding the required labeling for GE animals.

   We note that labeling of food from GE animals would be subject to the same requirements as food from non-GE animals, and that as with food from GE plants[3], the fact that the animal from which food was obtained was genetically engineered would not be material information with respect to labeling. However, if food from a GE animal is different from that of its non-engineered counterpart, for example if it has a different nutritional profile, in general that difference would be material information that would have to be revealed in labeling.

4. Components and Composition **(**21 CFR 514.1(b)(4))

   Section 514.1(b)(4) requires that an NADA include (1) a list of all articles used as components of the drug product; (2) a statement of composition of the drug product; and (3) a complete description of the fermentation of antibiotic drug substances.

   For GE animals, (3) would not be relevant. The information described in (1) and (2) should encompass the molecular characterization of the article. It should enable us to determine whether the article contains any potentially mobilizeable DNA sequences, and whether sequences are present that encode pathogens, toxicants, allergens, or substances likely to dysregulate the growth control of cells, tissues, or organs, except

[3] See, for example, FDA's 1992 "Statement of Policy: Foods Derived from New Plant Varieties" (57 FR 22984), and FDA's 2001 draft guidance "Voluntary Labeling Indicating Whether Foods Have or Have Not Been Developed Using Bioengineering" (http://www.cfsan.fda.gov/~dms/biolabgu.html).

by explicit design. We would expect that such information would describe the source, identity, purity, and functionality of the introduced article. For a more complete description of how we recommend you present this information in the NADA submission, please see Section IV.C., Steps 2 and 3.

5. Manufacturing Methods, Facilities, and Controls (21 CFR 514.1(b)(5))

   Section 514.1(b)(5) requires that an NADA include a detailed description of the methods used in and the facilities and controls used for the manufacturing, processing, and packing of the new animal drug.

   For GE animals, this information should encompass

   - the method by which the rDNA construct was introduced into the initial GE animal, including whether the initial GE animal was chimeric;
   - the breeding strategy used to produce the lineage progenitor. (A lineage progenitor is the animal from which the GE animals used for commercial purposes are derived); and
   - full characterization of the article and insertion site(s) once stabilized genomically, including the number and orientation of the rDNA construct. In particular, we recommend that you evaluate whether there is interruption of a coding or regulatory region (insertional mutagenesis).

   Information submitted to satisfy the requirements for finished product analytical controls and a stability program should include information demonstrating the durability of the genotype and phenotype—that is, whether the article is stably inherited, and the phenotype is consistent and predictable. This should include developing a sampling plan.

   For genotypic durability, we recommend that you use the results of studies demonstrating that the article is stably inherited. For the phenotypic durability portion of the plan, we recommend that you submit data on the consistency of the expressed trait (based on the intended use) over multiple generations. We recommend that, where feasible, you gather data on inheritance from at least two generations, preferably more, and recommend that at least two of the sampling points be from non-contiguous generations (e.g., F_1 and F_3).

Your plan should include a method of identity with sufficient discrimination to determine (1) whether a given animal contains the article, and (2) whether the article has significantly changed from that which was evaluated in the NADA (i.e., a detection method for your GE animal and article). For a more complete description of how we recommend you present this information in the NADA submission, please see Section IV.C., Steps 2, 3, and 5. We recommend that you consult with us on developing these plans.

We intend to issue additional guidance regarding the application of GMPs to GE animal NADAs.

6. Samples **(**21 CFR 514.1(b)(6))

   Section 514.1(b)(6) requires that samples of the new animal drug and articles used as components and information concerning them be submitted to CVM if requested.

   This requirement applies to NADAs for GE animals as it does to conventional new animal drug applications. Sponsors are encouraged to contact CVM to determine what samples (such as a genomic sample containing the article) should be provided.

   If FDA establishes a tolerance for the new animal drug, FDA will notify FSIS and provide it with a summary of the information and evaluation upon which it based the tolerance, and a method of analysis to be used to enforce the tolerance. FDA and FSIS are discussing how to adapt and improve existing communication procedures so that they will fully accommodate the needs of both agencies in addressing GE animals intended to go into the food supply.

7. Analytical Methods for Residues **(**21 CFR 514.1(b)(7))

   Section 514.1(b)(7) requires that an NADA include method(s) and data to enable determination of residues of the new animal drug in food-producing animals, except when data or other adequate information establish that it is not reasonable to expect the new animal drug to become a component of food at concentrations considered unsafe.

   The information that should be provided to satisfy this requirement for a GE animal application includes a method of detection that can be used to identify the rDNA construct in the GE animal.

8. Evidence to Establish Safety and Effectiveness **(**21 CFR 514.1(b)(8))

Section 514.1(b)(8) requires that an NADA include data/information to permit evaluation of the safety and effectiveness of the new animal drug product for the use as suggested in the proposed labeling. Section 21 CFR 514.1(b)(8)(iv) also requires that sponsors supply all information relevant to safety and effectiveness for a new animal drug, favorable and unfavorable.

Information relevant to the (1) target animal safety component of the NADA is described further in Step 4 of Section IV.C.; (2) food and feed safety component of the NADA is addressed further in Step 6 of Section IV.C., and (3) establishing effectiveness is described further in Step 7 of Section C.

We recommend that you contact the Center for help in determining the most efficient manner to submit all the above relevant information.

9. Veterinary Feed Directive **(**21 CFR 514.1(b)(9))

Section 514.1(b)(9) requires that in the case of NADAs for Veterinary Feed Directive (VFD) drugs the application must include three copies of the VFD in the format described in 21 CFR 558.6(a)(4).

This requirement is not applicable to NADAs for GE animals.

10. Supplemental Applications **(**21 CFR 514.1(b)(10))

Section 514.1(b)(10) requires that if an NADA is a supplemental application, such application must include full information on each proposed change concerning any statement made in the previously approved application.

This requirement applies to NADAs for GE animals as it does to conventional new animal drug applications. Sponsors seeking supplemental applications for a GE animal should contact CVM to determine how to prepare such an application.

11. Applicant's commitment **(**21 CFR 514.1(b)(11))

Section 514.1(b)(11) requires that an NADA include a commitment by the applicant that any labeling and advertising for the new animal drug is consistent with the conditions stated in the labeling which is part of the application.

This requirement applies to NADAs for GE animals as it does to conventional new animal drug applications. Sponsors should refer to 21 CFR 514.1(b)(11) for a complete description of the conditions of this commitment.

12. Additional commitments **(**21 CFR 514.1(b)(12))

Section 21 CFR 514.1(b)(12) requirements that are relevant to a GE animal NADA include commitments by the applicants that

i) the methods, facilities and controls described in section 514.1(b)(5) conform to the current good manufacturing practice (GMP) regulations in 21 CFR 211, and

ii) any nonclinical laboratory studies included in the application are conducted in compliance with good laboratory practice (GLP) regulations (21 CFR 58), or, if not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

FDA intends to issue further guidance on how to meet the GMP regulatory requirements for GE animals.

With regard to compliance with GLP regulations, the requirements to include a statement regarding compliance or noncompliance applies to NADAs for GE animals as it does to conventional new animal drug applications.

13. Environmental Assessment **(**21 CFR 514.1(b)(14))

Section 514.1(b)(14) requires that an NADA include either a claim for categorical exclusion or an environmental assessment (EA). An EA must be prepared for each agency action except when the action is categorically excluded by 21 CFR 25.30 – 34 and no extraordinary circumstances exist. 21 CFR 25.21. The EA is a public document that provides sufficient information to allow FDA to either prepare an environmental impact statement (EIS) or issue a finding of no significant impact (FONSI). The specific information required for an EA is outlined in 21 CFR 25.40. This requirement applies to NADAs for GE animals as it does to conventional new animal drug applications.

An EA that demonstrates the GE animal will not significantly affect the quality of the human environment leads to a finding of no significant impact (FONSI). We recommend that the EA focus on environmental issues and potential impacts related to the use and disposal of the GE animal and its final product, if relevant. The appropriate scope and

content of the EA may vary widely depending on the GE animal product, claim, and conditions of use. Therefore, we recommend that you contact and work closely with us on these issues before proceeding with preparation of the EA, which is described in more detail in Step 6 of Section C.

14. Assembling and Binding the Application **(**21 CFR 514.1(b)(15))

Section 514.1(b)(15) describes certain administrative requirements for submitting an NADA to FDA. These requirements apply to NADAs for GE animals as they do to conventional new animal drug applications. We recommend that you contact CVM for further guidance on assembling your NADA.

C. Recommended Process for Completing Pre-approval Assessments for GE Animals

To facilitate the evaluation of GE animals under the existing regulatory framework for new animal drugs, we have developed the following approach for submitting data for an NADA for GE animals. It fulfills the regulatory requirements described in the preceding section and helps guide sponsors in developing their regulatory submission strategies.

This approach is cumulative and risk-based. Each component of the assessment forms the basis on which the next step is evaluated. The approach is risk-based because it examines both the *potential hazards* (that is, components that may cause an adverse outcome) identified at each step along the pathway and the *likelihood of harm* among the receptor populations (the GE animals themselves as well as those individuals or populations exposed to the GE animals). It is also conducted on a case-by-case basis, because the potential hazards and risks are likely to be unique to each application.

We encourage you to consult with us as you develop data to satisfy the elements below, to ensure that the process is as efficient as possible and that the data and information you provide is in a format that will facilitate our ability to review it.

Step 1: Product Identification

Product identification (21 CFR 514.1(b)(1)), which many molecular biologists would refer to as product definition, forms the foundation for the evaluation process and drives subsequent data generation and review. It encompasses the specific GE animal (that is, the article as well as the GE animal containing it) and the purpose (i.e., intended use) of

the article that is the subject of the NADA. We believe that the concept of product identification is so important to the structure and content of the NADA submission that we encourage you to consult us on this topic as early as possible in the GE animal development process, for example as an early part of the INAD process.

A product definition characterizes the GE animal. Therefore, as indicated in section IV.B.1, we recommend that the product identification include the following information:

- Ploidy of GE animal;
- Zygosity of GE animal;
- Description of the animal (e.g., common name/breed/line; genus and species);
- Number of copies of the rDNA construct;
- Construct name;
- Characterization of the insertion site(s);
- Name of GE animal line; and
- The intended use or claim being made for the GE animal.

Step 2: Molecular Characterization of the Construct

This step of the process serves to describe the components and composition of the article. (21 CFR 514.1(b)(4).) For this step, we recommend that you provide information for identifying and characterizing the rDNA construct that will be introduced into the progenitor of the GE animal that will be marketed. This and the next step in the process are part of the hazard identification component of the safety review of the NADA. (21 CFR 514.1(b)(8)). Typically, the information should include, but not be limited to the following:

- a description of the source(s) of the various functional components of the construct;
- the sequence of the rDNA construct;
- the purpose of the modification;
- details of how the rDNA construct was assembled;

- the intended function(s) of the introduced DNA; and
- the purity of the preparation containing the rDNA construct prior to introduction into recipient animals or cells.

In order to determine whether any risks exist that would make the product unsafe, we expect to evaluate whether the rDNA construct contains any potentially mobilizeable DNA sequences, or whether sequences are present that encode pathogens, toxins (including allergens), or substances likely to dysregulate the growth control of cells, tissues, or organs, except by explicit design.

Step 3: Molecular Characterization of the GE Animal Lineage

This step continues the analysis of the rDNA construct in the resulting GE animal, as well as the production of the GE animal(s) intended to be used in commerce and any potential hazards that may be introduced into those animals as part of their production. As such, this step addresses the identity and some manufacturing requirements of your NADA. 21 CFR 514.1(b)(1) and (b)(5). We recommend that you provide data and information describing the method by which you introduced the rDNA construct into the initial GE animal, including whether the initial GE animal was chimeric. In addition, we recommend that you describe the breeding strategy you used to produce the lineage progenitor (the GE animal that contains the final stabilized version of the initial event and from which the GE animals to be used for commercial purposes are derived). You should fully characterize the final stabilized rDNA construct in the GE animal.

Step 4: Phenotypic Characterization of GE Animal

The previous steps of the review process have concentrated on establishing and characterizing the rDNA construct and its integration into the resulting GE animals. Information in this and the following steps helps establish whether the GE animal poses any risks to humans, risks to health of the GE animal, or risks to the environment.

With regard to health of the GE animal, including the target animal safety requirements of 21 CFR 514.1(b)(8), we recommend that you submit data regarding whether the rDNA construct or its expression product(s) cause any direct or indirect toxicity. In general, we recommend that you compile and submit data and information addressing the health of the GE animals, including veterinary and treatment records, growth rates, reproductive function, and behavior. In addition, we recommend that you submit data on the

physiological status of the GE animals, including clinical chemistry, hematology, histopathology, and post-mortem results. We recommend that you collect data from a generation of GE animals as close as possible to that intended for use in commerce.

Step 5: Genotypic and Phenotypic Durability Assessment

As in Step 3, this step also addresses some additional components of the manufacturing requirements codified in 21 CFR 514.1(b)(5). It is intended to provide information to ensure that the rDNA construct in the GE animal resulting from the specific transformation event and defining (identifying) the GE animal being evaluated is durable — that there is a reasonable expectation that the rDNA construct is stably inherited, and the phenotype is consistent and predictable. This would include developing a sampling plan.

For genotypic durability, we recommend that you use the results of studies demonstrating that the rDNA construct is stably inherited. For the phenotypic durability portion of the plan, we recommend that you submit data on the consistency of the expressed trait (based on the intended use) over multiple generations. We recommend that, where feasible, you gather data on inheritance from at least two generations, preferably more, and recommend that at least two of the sampling points be from non-contiguous generations (e.g., F_2 and F_4).

Your plan should include a method of identity with sufficient discrimination to determine (1) whether a given animal contains your construct, and (2) whether the construct has significantly changed from that which was evaluated to be safe and effective (i.e., a detection method for your GE animal including the rDNA construct in its final stabilized genomic location(s)). We recommend that you consult with us on developing these plans.

Step 6: The Food/Feed Safety and Environmental Safety Assessments

Food/Feed Safety

This part of Step 6 addresses the food and feed safety requirements in 21 CFR 514.1(b)(8). It focuses on the issue of whether food or feed derived from a GE animal is safe for humans or animals consuming edible products from the animals.

The risk issues involved in determining food and feed safety can be divided into two overall categories. The first addresses whether there is any direct toxicity, including

allergenicity, via food or feed consumption of the expression product of the article. The second category addresses potential indirect toxicity associated with both the article and its expressed product (e.g., whether location or expression of the article affects physiological processes in the resulting animal such that unintended food/feed consumption hazards are created, or whether existing food/feed consumption risks are increased). Potential adverse outcomes via the food/feed exposure pathway should be identified by determining whether there are any biologically relevant changes (1) to the physiology of the animal (assessed partly in *Step 3: Phenotypic Characterization of the GE Animal*), and (2) in the composition of edible tissues from the GE animal that suggest reason for toxicological concern compared with the appropriate non-GE comparator.

In the end, if the expression product(s) is shown to be safe, and the composition of edible tissues from the GE animal is shown to be as safe as those from animals of the same or comparable type that are commonly and safely consumed, then we expect to view this as evidence that food and feed derived from the GE animal is safe (i.e., there is a reasonable certainty of no harm from consumption of the food or feed).

Food from GE animals is subject to the same labeling requirements as other foods. With respect to food from animals, FDA regulates labeling of fish and seafood, of milk and other dairy products, and of whole eggs in their shells. FSIS has oversight of labeling of most meat, poultry, and egg products. In situations in which food from a GE animal is different from that of its non-engineered counterpart, for example if it has a different nutritional profile, in general that difference would be material information that would have to be revealed in labeling.

FDA participated in the Codex *ad hoc* Intergovernmental Task Force on Foods Derived from Biotechnology and its Working Group that developed the recently adopted guideline for assessing food safety of foods from rDNA animals (Codex Alimentarius Commission: *Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Animals; in* ALINORM 08/31/34, Appendix II; (ftp://ftp.fao.org/codex/Alinorm08/al31_

34e.pdf). The information needed to establish food safety for food from GE animals under an NADA is consistent with that described in the Codex Guideline.

Environmental Safety

This portion of Step 6 addresses the environmental component of your NADA. 21 CFR 514.1(b)(14). We expect that, at least until we have more experience, most GE animal applications would have to be evaluated to determine whether such an application individually or cumulatively affects the environment (i.e., whether an extraordinary circumstance exists). 21 CFR 25.21. An EA that demonstrates the GE animal will not significantly affect the quality of the human environment leads to a finding of no significant impact (FONSI).

We recommend you contact us early in the development of your GE animal so that we can focus the EA on the environmental issues and potential impacts related to the use and disposal of your GE animal and its final product, if relevant. The appropriate scope and content of the EA may vary widely depending on the GE animal product, claim, and conditions of use (e.g., aquatic vs. terrestrial animal species). Therefore, we recommend that you contact and work closely with us on these issues before proceeding with preparation of the EA.

Step 7: Effectiveness/Claim Validation

The previous steps of the review process primarily address identity and safety issues. This last step of pre-market review addresses effectiveness, i.e., whether you have validated your claims for the characteristics that the GE animal is intended to exhibit. 21 CFR 514.1(b)(8). For example, in the case of a GE animal that is intended to resist disease, you should demonstrate that the GE animals were indeed resistant to that disease. In the case of GE animals that are intended to produce a non-food product, you should demonstrate that the animal indeed produces the claimed product. If that product is, for example, a drug or component of a drug intended for use in humans, the safety and effectiveness of that drug would be evaluated separately by Center for Drug Evaluation and Research. We recommend that you work closely with us to determine the nature and extent of data to meet these requirements.

V. Post-Approval Responsibilities

Once a GE animal is approved, sponsors have on-going responsibilities including registration and drug listing, recordkeeping, filing supplements, and periodic reporting. (21 USC 360, 21 USC 356a, 21 CFR 514.80, 21 CFR 514.8). We recommend that you use the following general approach to fulfill these requirements, but that you work closely with us in order to determine the specific data and information to submit.

A. Statutory Registration and Drug Listing Requirements

As part of the registration requirements under 21 USC 360, you are required to register your name and place of business, and identify any facility(ies) engaged in the production or testing of the GE animal. See 21 CFR Part 207. As part of your listing responsibilities, you are required to list all regulated articles, 21 CFR 207.22(a)(1), which should be a list of all GE animal lines you have produced.

B. Recordkeeping

You must establish and maintain indexed and complete files containing full records of all information relevant to the safety or effectiveness of a GE animal that has not been previously submitted as part of the NADA. 21 CFR 514.80(a)(1). This would generally consist of Adverse Event Reports or other data or information from domestic or foreign sources, such as published literature.

C. Annual Reports, Supplements, and Other Changes to an Approved Application

We recommend that information demonstrating genotypic and phenotypic durability be collected from a subset of marketed approved GE animals on an annual basis. You should consult with us on the nature of the information to be collected, as it will be determined on a case-by-case basis. We also recommend that you maintain current standard operating procedures (SOPs) for each test method employed. In addition, we recommend that you maintain SOPs for other procedures used in the husbandry of GE animals (e.g., those resulting in biological containment).

You must submit information on all changes that have been made, or that you propose to make to the GE animal (21 CFR 514.8(b)). Depending on the risk(s) that could be introduced by that change, the nature and timing of the reporting may be different. Information on the types of changes and which type of reporting they require are found in 21 CFR 514.8. We anticipate issuing a separate guidance addressing post-market

reporting issues for GE animals. We recommend contacting us if you have any questions regarding determining the category in which your changes may fall.

D. Records and Reports Concerning Experience with Approved Products

You are required to submit reports of data, studies, and other information of experience with the GE animal. 21 CFR 514.80(a)(2). These experience reports must be submitted to our Division of Surveillance every six (6) months for the first two years following approval, and annually thereafter. 21 CFR 514.80(a)(4).

We remind you that the labeling associated with a GE animal may only prescribe, recommend, or suggest use under the conditions approved in the labeling that was submitted as part of the approval. 21 USC 360b(a)(1). This labeling must use the same language and emphasis as in the approval, including descriptions of relevant hazards and precautions.

VI. Import Tolerances

Section 512(a)(6) of the Act enables FDA to establish a safe level of new animal drugs and drug residues in edible portions of animals (i.e., food) imported into the United States (an import tolerance) when those drugs have not been approved for use in the United States. Whether a sponsor seeks approval of an NADA for a GE animal or establishment of an import tolerance for food from a GE animal, the food safety standard is essentially the same.[4] Information about import tolerances, which enable imports of such food from GE animals developed outside the United States, is found in the sections of this guidance relevant to evaluating food safety and would be consistent with the recommendations in the Codex *Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Animals*. We recommend that you consult with us on establishing an import tolerance.

[4] To establish an import tolerance, FDA must review data showing that the tolerance is safe based on food safety criteria similar to those used for a full NADA approval.