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Heritable Intentional Genomic Alterations in Animals of Food-Producing Species for Use as Models of Disease

Guidance for Industry

Draft Guidance

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Additional copies of this draft guidance document may be requested from the Policy and Regulations Staff, Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville MD 20855, and may be viewed on the Internet at https://www.fda.gov/animal-veterinary, https://www.fda.gov/regulatory-information/search-fda-guidance-documents, or http://www.regulations.gov.

U.S. Department of Health and Human Services
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Center for Veterinary Medicine (CVM)
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Heritable Intentional Genomic Alterations in Animals of Food-Producing Species for Use as Models of Disease[1]

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. Introduction

This draft guidance for industry (GFI) sets forth the Food and Drug Administration's (FDA, Agency, we) policy regarding heritable intentional genomic alterations (IGA) in animals of food-producing species (e.g., swine, rabbits)[2] that are intended to be marketed for use as models of human or animal disease in biomedical research under contained and controlled conditions.[3] This guidance reflects FDA's current thinking regarding such products and describes the conditions under which FDA generally does not expect people or companies developing IGAs in animal models of disease (developers or you) to submit an application or get our approval prior to marketing following a prior review of risk factor data.

In general, FDA's guidance documents 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. Background

FDA GFI #187A, entitled "Heritable Intentional Genomic Alterations in Animals: Risk-Based Approach," clarifies that heritable IGAs in animals are subject to FDA oversight and that the Agency applies a risk-based regulatory approach to these products. The subject of this draft guidance is IGAs in animals of food-producing species that are intended to be marketed for use as models of human or animal disease in biomedical research under contained and controlled conditions ("IGAs in animal models of disease"). This research may be basic research of general

[1] This draft guidance has been prepared by the Center for Veterinary Medicine (CVM) in consultation with the Office of Inspections and Investigations (OII) at the Food and Drug Administration.

[2] For purposes of this guidance, if a species, such as swine, is food-producing, then all members of that species are considered food-producing even if particular breeds or lines are not ordinarily raised for food.

[3] Note that animals with IGAs that are intended to produce tissues for use in xenotransplantation are not within the scope of this guidance.

applicability (e.g., understanding the underlying pathophysiology of a disease or disease processes) or it may be research or pre-clinical testing for a particular medical product that may support an application for product approval (e.g., preclinical trials of safety or effectiveness in altered animal models closely resembling human disease). In either case, the developer plans to market the animals for use in this research.

GFI #187A states that, "while, in general,[4] FDA approval of IGAs in animals is required…in some circumstances we do not expect the people or companies developing" certain IGAs in animals to submit an application or obtain approval of an application prior to marketing their product following prior review of risk factor data. Among these IGAs are those that GFI #187A describes as Category 2. These are IGAs for which we may not expect developers to submit an application for approval if, after analyzing data submitted about the products' risks, we find we understand the product's risks for the specified intended use, any identified risks, including their potential severity and likelihood of occurring, are appropriately mitigated, and we have no further questions for which we would need to see additional data to address.

As described in GFI #187A, for Category 2 determinations, CVM generally intends to review information submitted to a veterinary master file (VMF), which does not trigger a developer to be defined as an animal drug sponsor subject to user fees.[5] Draft GFI #260, "Type VII Veterinary Master File for Research and Development and Risk Reviews," if finalized, will provide further information on circumstances where CVM generally does not expect developers to open an investigational file under 21 CFR 511.1 but instead open a Type VII VMF.

In this draft guidance, we address those circumstances and conditions under which we may not expect developers to submit an application for approval of an IGA in an animal model of disease if, after looking at data submitted about that product's risk, we determine that it appropriately fits in Category 2. FDA believes that IGAs in animal models of disease are likely to fit in Category 2 in part because the animals are unlikely to enter the food supply or to escape and establish in the environment. For these reasons, based on case-by-case evaluation of data and information as described below, we may determine that IGAs in animals intended as models of disease are in Category 2, and we do not expect developers of these IGAs to submit an application for approval to us prior to marketing.

However, we expect that animals with such IGAs will express the anticipated phenotypic characteristics. Also, we do retain the discretion to take action, if warranted, to address any safety concerns associated with these IGAs in animals. We also anticipate that other technologies intended to alter genomic DNA will arise over time. We intend to update this guidance to reflect newer technologies, as well as improvements to existing technologies, as necessary.

For information on whether the IGA in an animal you are developing is within the scope of the policy set forth in this guidance document or if, instead, you should establish an investigational

[4] FDA does not intend to regulate IGAs in animals that meet the definition of a veterinary biologic and are regulated by the Animal and Plant Health Inspection Service (APHIS) of the United States Department of Agriculture (USDA) (21 CFR 510.4).

[5] Section 739(6) of the FD&C Act (21 U.S.C 379j-11(6))

file under 21 CFR 511.1, you should contact CVM early in the development process. Note that any inquiries or information you submit to us at this early stage should be submitted to a Veterinary Master File, which does not require you to pay user fees, rather than an investigational file. CVM will keep confidential any confidential commercial information and trade secrets in material that you submit as required by law.

III. Policy

FDA intends to use our resources in a way that protects public and animal health by taking a different approach for different IGAs in animals based on the level of risk associated with them, meaning how well we understand the IGA or type of IGA as well as its intended use. For IGAs in animal models of disease, we will evaluate data and information you submit to address the risk factors described below and determine whether we agree that your product is appropriate for Category 2 and we do not expect you to open an investigational file or submit an application for approval.

As a general matter, the questions we intend to consider when determining whether an IGA in an animal model of disease may be appropriate for Category 2 include, but are not limited to, the following:

1. Safety (Human, Animal, and Environmental)

- Is there anything about the IGA itself that may pose an unintentional human, target animal, or environmental risk?[6]

- Does the IGA contain new sequences or delete existing sequences that can indirectly affect the health of the animal (e.g., create a disease condition other than the intended one)?

- Is there anything unique about the IGA or the resulting altered animals that may result in unintended effects such as human handler risks, risks to its surrogate dam (i.e., the embryo recipient animal), or to the animal itself (e.g., does the introduction of a gene intended to cause increased susceptibility to unregulated growth, such as neoplasia, also pose a risk of excessive non-neoplastic growth of non-target tissues such as muscle or bone)?

- Is appropriate control and oversight in place to ensure the adequate health and

[6] The National Environmental Policy Act (NEPA) requires that Federal agencies consider the environmental impacts of any "major Federal action" that it takes (42 U.S.C. § 4332(c)). Approval of an application is a major Federal action that triggers the requirement for environmental analysis under NEPA (21 CFR 25.33). However, a decision not to enforce investigational, approval, or other requirements is not a "major Federal action." See *Int'l Ctr. for Tech. Assessment v. Thompso*n, 421 F. Supp. 2d 1 (D.D.C. 2006). While NEPA review is not required for a Category 2 determination, environmental risks are among the factors we intend to consider in making this risk-based determination.

well-being of the altered animals?[7]

- Are there concerns over the disposition or disposal of the anticipated number of animals with the IGA that the developer will produce that could pose human, animal, or environmental risks?

2. Exposure/Release Risk (Containment, Food Safety, Shipping, and Disposal)

- Are there data and information, including standard operating procedures (SOPs) to demonstrate that:
    - The altered animals are adequately contained in their physical facilities;
    - The altered animals have multiple forms of identification; and
    - There is a practicable method to identify the IGA in the altered animal, or in food derived from the altered animal in the event of an inadvertent release or escape?
- Is there a developer commitment to keep the altered animals out of the human and animal food supply, including SOPs for disposal by incineration, burial, composting, or some other means that FDA finds acceptable?[8]
- In the event of shipping these animals to others:
    - Do SOPs and/or material transfer agreements (MTAs) require documentation of shipping of altered animals?
    - Do SOPs and/or MTAs ensure that the altered animals are kept out of the human and animal food supply, including having systems in place to ensure appropriate disposition of animals, carcasses, and materials derived from the animals?[9]

3. Other Safety Issues

- Have either the developer of these IGAs in animals, or any recipients of the animals encountered unanticipated safety issues?

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[7] Developers must follow all applicable Federal and State requirements, including the requirements of the Animal Welfare Act, which are administered by the U.S. Department of Agriculture (7 U.S.C. §§ 2131-2159; 9 CFR parts 1-3). The Animal Welfare Act requires Institutional Animal Care and Use Committee approval and oversight of applicable animal research.

[8] If such altered animals were to enter the food supply, the food would be considered adulterated under section 402(a)(2)(C)(ii) of the FD&C Act.

[9] As noted in footnote 7, any food derived from such altered animals would be adulterated under the FD&C Act.

On a case-by-case basis, we will evaluate these factors for IGAs in animal models of disease and make a Category 2 determination. We intend to make these determinations and send you a written response within 180 days. Our written response will either inform you that: (1) based on our review for that IGA, we find that we understand the product's risks for the specified intended use, any identified risks are appropriately mitigated, and we have no further questions for which we would need to see additional data to address and we, therefore, believe the IGA is appropriate for Category 2 and do not expect submission of an approval application; or (2) we find that you have not adequately addressed each of these factors and the IGA is not appropriate for Category 2.