

**#187A**

# **Heritable Intentional Genomic Alterations in Animals: Risk-Based Approach**

## **Guidance for Industry**

*This guidance, together with companion Draft Guidance #187B, “Heritable Intentional Genomic Alterations in Animals: The Approval Process,” is a revision of Guidance #187, “Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs,” which has been revised to update information concerning the products of different technologies used to produce such animals, and to provide new weblinks.*

Submit comments on this guidance at any time. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number FDA-2008-D-0394.

For further information regarding this document, contact [AskCVM@fda.hhs.gov](mailto:AskCVM@fda.hhs.gov).

Additional copies of this guidance document may be requested from the Policy and Regulations Staff (HFV-6), 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  
Food and Drug Administration  
Center for Veterinary Medicine (CVM)  
May 2024**

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# **Heritable Intentional Genomic Alterations in Animals: Risk-Based Approach**

## **Guidance for Industry**

*This guidance represents the current thinking of the Food and Drug Administration (FDA, Agency, or we) 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 and Background**

FDA is issuing this revised Guidance for Industry (GFI) to clarify our risk-based approach to heritable intentional genomic alterations (IGAs) in animals.<sup>1</sup> As described below, a risk-based approach means that the scope of FDA’s review and data expectations are commensurate with the risk profile of the product. In order to make our guidance clearer and more streamlined, we are issuing this guidance document in two parts: GFI #187A, “Heritable Intentional Genomic Alterations in Animals: Risk-Based Approach,” to articulate our policy on our risk-based approach to oversight of IGAs in animals; and a companion draft guidance document, GFI #187B, “Heritable Intentional Genomic Alterations in Animals: The Approval Process”<sup>2</sup> (Draft GFI #187B), to provide more technical guidance for developers of those IGAs in animals that go through FDA’s approval process prior to marketing.

IGAs in animals are intentional genomic alterations made using modern molecular technologies, which may include random or targeted DNA sequence changes, including nucleotide insertions, substitutions, or deletions, or other technologies that introduce specific changes to the genome of the animal.<sup>3, 4, 5</sup> Some of the more commonly used terms for types of modern molecular technology currently being used to make IGAs are “genetic engineering” and “genome editing,” but there may be other types of modern molecular technology developed over time that can make

<sup>1</sup> Non-heritable intentional genomic alterations in animals are outside the scope of this guidance document.

<sup>2</sup> <https://www.fda.gov/media/150658/download> (May 2024).

<sup>3</sup> FDA used the term “genetically engineered” (GE) to describe the animals within the scope of the version of Guidance for Industry #187 published January 2009. The term “GE” does not suit the discussion in this revised guidance because this guidance’s scope includes IGAs in animals that are produced with newer technologies. The term “transgenic” is also not used for the same reason, except for citation of earlier documents.

<sup>4</sup> In Guidance for Industry #236, “Clarification of FDA and EPA Jurisdiction Over Mosquito-Related Products,” FDA clarified that articles intended to function as pesticides by preventing, destroying, repelling, or mitigating mosquitoes for population control purposes are not regulated under FDA’s authority. Rather, the Environmental Protection Agency regulates products intended to function as pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. § 136 et seq.). (<https://www.fda.gov/media/102158/download> (October 2017).)

<sup>5</sup> The term “modern molecular technologies” does not include induction of polyploidy by heat, pressure, or chemical treatment or selective breeding or other assisted reproductive technologies. These methods are outside the scope of this guidance document.

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intentional genomic alterations (see more detailed information below). These technologies hold great promise for many uses and public and animal health benefits, such as animal disease resistance, control of zoonotic disease transmission to humans, improved animal welfare, and increased and higher quality food production. Developers are also using these technologies to make improvements in animals that will benefit human health, such as through production of animals that are less allergenic, production of animals that will serve as models of human disease for research and development of human therapies, and the development of innovative human medical products that are produced or derived from animals with IGAs. FDA is committed to using an appropriate, risk-based approach based on sound science and risk assessment review processes to further the advancement of this field for the development of safe and effective products, while supporting consumer confidence.

Recombinant DNA (rDNA) technology has been used for the past 50 years to intentionally alter traits in microorganisms,<sup>6</sup> and 40 years for plants, and animals. Various agencies across the U.S. Government have provided guidance and regulation to affected stakeholders describing the regulation of these altered organisms and the products of those alterations. Historically, rDNA techniques involved splicing DNA sequences from various sources and introducing them into animals via techniques that resulted in random integration events. In 2009, FDA explained our regulatory approach at that time in the original version of GFI #187, “Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs.”<sup>7</sup>

Newer technologies have emerged that are used to intentionally alter the genomes of various organisms, including animals. Some of these technologies include the use of “nucleases” or “genome editing technologies,” including engineered nuclease/nucleotide complexes such as zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and the clustered regularly interspaced short palindromic repeats (CRISPR) associated systems.<sup>8</sup> These nucleases are intended to introduce alterations at specific sites in the genome, rather than the more randomly located changes associated with rDNA technology. The selectivity and specificity of these techniques continues to improve. The process of producing these targeted DNA sequence alterations is often referred to as “genome editing.” This guidance clarifies the scope of the version of GFI #187 FDA issued in 2009 to include IGAs created with these newer technologies and thus includes IGAs produced using rDNA technology as well as newer genome editing and other technologies. We anticipate that, over time, IGAs created with other technologies will arise. This policy is being implemented based on the Agency’s current understanding of these products and their risk(s). We may update this guidance as needed, should our scientific understanding of these products and their risk(s) change and/or to reflect newer technologies as well as improvements to existing technologies.

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<sup>6</sup> See e.g., Cohen SN, Chang AC, Boyer HW, Helling RB. Construction of biologically functional bacterial plasmids in vitro. *Proc Natl Acad Sci U S A*. 1973;70(11):3240-3244. doi:10.1073/pnas.70.11.3240.

<sup>7</sup> <https://wayback.archive-it.org/7993/20161022005328/http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM113903.pdf> (June 2015).

<sup>8</sup> For a more complete description of genome editing techniques, see Maxmen A. Three technologies that changed genetics. *Nature Outlook* Special Supplement Vol. 528, S2-S3, 3 December 2015, doi: 10.1038/528S2a.

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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. FDA's Approach**

### **A. What We Oversee and Why**

FDA is responsible for ensuring that IGAs in animals are safe and effective. To do this, we use a risk-based regulatory approach. This means we won't expect the people or companies developing certain types of IGAs in animals to submit an application for approval before marketing their product.<sup>9, 10</sup> These are IGAs in animals and animal products for which 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. We explain how this works and the types of risks we look at below in section [B.1.b. Category 2: Prior review of risk factor data](#). For these types of IGAs, we may decide, either without prior review or based on a review of data addressing risk factors as described below, that we do not expect developers to seek approval of these IGAs. For IGAs that do go through the approval process, FDA approves those that it determines are safe to the animal, safe to anyone that eats food derived from the animal if it is a food-producing animal, and do what the developer claims it will do, i.e., the product is safe and effective. FDA's approach is risk-based because it examines both the *potential hazards* (i.e., components that may cause an adverse outcome) identified throughout the review and the *likelihood of harm* among the receptor populations (i.e., the IGAs in animals themselves, as well as those individuals or populations exposed to these animals).

An IGA may be the result of random or targeted DNA sequence changes (nucleotide insertions, substitutions, or deletions or other specific changes to the genome of the animal). The article we are regulating is the specific DNA alteration at each site in the genome where the intended alteration (i.e., insertion, substitution, or deletion) occurs. Our review of the article includes evaluation of the site(s) of intentional alteration as well as whether the introduction of the intended alteration also results in any unintended alterations (e.g., alterations at identified potential off-target sites, unanticipated insertions, substitutions, or deletions) and, if so, their effects. The specific sequence that is being altered and the location of the alteration can impact both the health of the animals and the effectiveness of the IGA (for example, random insertions/deletions designed to knock out a protein may result in low levels of the protein still being expressed, which may result in the IGA not doing what it is supposed to do). This does not mean that every alteration requires a separate FDA review or approval. As we describe in

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<sup>9</sup> The product is the IGA and the marketed item(s) containing the IGA (e.g., eggs, semen, embryos, live animals, etc.).

<sup>10</sup> This is based on a decision under section 301(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) [21 U.S.C. § 331(a)] as a matter of enforcement discretion not to take action against a developer for the introduction or delivery for introduction into interstate commerce of an IGA in an animal under the "Category 1" and "Category 2" circumstances described below.

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Draft GFI #187B, FDA can review and/or approve one application for more than one alteration in an animal and for multiple lineages in the same species of animal. Also, as we explain in Draft GFI #187B, we don't expect developers to get our approval of an IGA in offspring of animals that contain different approved IGAs or the offspring of an animal with an approved IGA and an animal with no IGA. We note also that while FDA approvals are specific to the particular sponsor's product that is the subject of the approval application, our reviews of IGAs are informed by previous reviews. As a result, if we receive applications for similar IGAs with the same or similar intended uses, while we cannot rely on data from a previous review of a different product, based on our increased understanding after the initial approval, FDA's review may be more efficient.

### **B. Risk-Based Approach**

We intend 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 risk associated with them. Where the risk is best understood and mitigated (Category 1), we don't expect developers to consult with us on the risk of their product prior to marketing the animal. At the next level (Category 2), we may not expect developers to submit an application for approval of an IGA if, after analyzing data submitted about that product's risk, we find that 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. At the third level (Category 3), FDA will review and, where the data supports it, approve a product using data requirements that are proportionate to the risk of that particular product. For those products in Category 3, as FDA and the scientific community gain more understanding and experience with IGA products in animals and the technology becomes more precise, the assessment of potential risks they pose may be diminished, so that we may decide that some IGAs in Category 3 are understood well enough that they may fit in Category 2 and, at that time, developers would not be expected to submit applications for approval prior to marketing animals containing such IGAs.

For guidance on FDA's investigational and approval requirements related to IGAs in animals, see Draft GFI #187B.

In summary, what this means is that while, in general,<sup>11</sup> FDA approval of IGAs in animals is required, as we describe below, in some circumstances we do not expect the people or companies developing Category 1 IGAs in animals to submit information to FDA and, for Category 2 IGAs in animals, while we expect submission of information to establish the IGA meets the Category 2 description below, we would not expect developers to submit an application for approval prior to marketing their product.<sup>12</sup> This determination is not a finding of "safety" under the Federal Food, Drug, and Cosmetic Act (FD&C Act); rather, we are deciding whether the product fits

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<sup>11</sup> 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.

<sup>12</sup> In this circumstance, and throughout this guidance, where FDA states that it may not expect a developer to seek approval, we mean that, on a case-by-case basis, FDA does not intend to take action for the introduction or delivery for introduction into interstate commerce of an unapproved IGA in an animal.

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appropriately within Category 2 because, as described above, we understand the product's risks for the specified intended use and have concluded we have no safety concerns. Consequently, we find it appropriate to exercise enforcement discretion over approval requirements for that product.<sup>13, 14</sup> We generally do not make these types of decisions about products based on the technology used or the size or type of the genomic alteration made (e.g., single base pair changes v. large deletions; insertions v. deletions). If you are developing an IGA that you think may be a candidate for enforcement discretion as described below, we encourage you to come talk to us about your product development plans so we can begin the discussion about the appropriate level of regulatory oversight for your product.

### **1. Enforcement Discretion: No Application Expected**

#### **a. Category 1: No application expected, no prior review**

Consistent with our past practice, FDA may decide that we don't expect submission of an application for approval or submission of data on risk profile<sup>15</sup> for: (1) IGAs in animals of nonfood-producing species that are regulated by other Federal government agencies or entities, such as insects with intentionally altered genomes that are regulated by APHIS<sup>16</sup>; and (2) animals of nonfood-producing species that are raised and used in contained and controlled laboratory conditions for research (e.g., mice and rats). FDA believes that these IGAs are either already adequately regulated or that they pose negligible risk because the animals containing them aren't likely to end up in the food supply or to get out into the environment. This means that we do not expect developers of this type of IGA to come to us for our approval prior to marketing.<sup>17</sup>

#### **b. Category 2: No application expected following prior review of risk factor data**

There may be other IGAs in animals, including food-producing animals, that FDA determines meet the Category 2 description and we also wouldn't expect developers to submit an application for approval to market these types of IGAs in animals. Note, though, that if you wish to introduce food derived from animals with IGAs into the food supply prior to our determination that an IGA you are developing in a food-producing animal fits in Category 2, we expect you to

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<sup>13</sup> This is based on a decision under section 301(a) of the FD&C Act [21 U.S.C. § 331(a)] as a matter of enforcement discretion not to take action against a developer for the introduction or delivery for introduction into interstate commerce of an IGA in an animal in the particular situation described.

<sup>14</sup> See [FDA statement re: SLICK cattle](#).

<sup>15</sup> *Id.*

<sup>16</sup> USDA APHIS has regulated under its Plant Protection Act authority, 7 U.S.C. § 7701 *et seq.*, insects with intentionally altered genomes. FDA and USDA will consult to determine the appropriate regulatory approach for invertebrates with intentionally altered genomes that are subject to APHIS' Animal Health Protection Act authority 7 U.S.C. § 8301 *et seq.*

<sup>17</sup> As of the date we issued this guidance document, we are not aware of any safety concerns for this category of IGAs in animals and FDA has determined that they are of negligible risk and that these products do not require additional regulatory oversight at this time. We do retain the discretion to take action, if warranted, to address any safety concerns we learn about that are associated with these IGAs in animals.

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get prior authorization to do so through the investigational food use authorization process (21 CFR 511.1(b)(5)).

In order to decide whether IGAs (in addition to those described above) fit within Category 2, we will evaluate risk factors for the particular type of IGA in animals as described below. To support the evaluation of potential risk factors, developers generally submit data and information based on an appropriate comparator for the intended use (e.g., an unmodified comparator of the same species). This includes information about the methodology used to generate the IGA, characterization of the genomic sequence, and information addressing animal safety, food safety, and risk of impacts on the environment, as appropriate for the intended use of the product, as the types of risks we are concerned with will vary for particular products depending upon the nature of the IGA, the species of animal, and other factors specific to each product.<sup>18</sup> For example, information about the methodology used to generate an IGA informs the appropriate approach to molecular characterization, as the methodology may affect the nature of unintended impacts (e.g., when an rDNA construct is intended to be targeted to a specific site, unintended integration events should be screened for, while for genome editing, an analysis of potential unintended alterations at the target site or elsewhere in the genome should be evaluated). For food safety, the type of factors we might look at include whether the IGA may result in an elevated level of hormones, proteins or production of novel substances that could be harmful to human health if consumed, and whether the nutritional composition of the food is altered. For animal safety, we might be concerned with potential changes in an animal's physiology or behavior that interfere with its basic functioning or cause suffering or a potential for elevated susceptibility to disease. For environmental factors we might be concerned with the ability of altered animals to establish in the environment.

In general, we intend to make decisions on risk determination questions and send you a written response within 180 days of your request for a Category 2 determination and enforcement discretion decision. We have [a list](#) on our website of IGAs in animals for which we have already made this risk evaluation and decided are in Category 2 and for which we are exercising enforcement discretion. Where we have permission from the developer, the list also includes a link to a summary of the types of data and information we evaluated and our conclusions for those products that are for food use or first of their kind on the market. We will keep adding to this list over time. While we believe it is unlikely that risks for the IGA products on the list would increase, if they did we would reevaluate whether the IGA should remain on the Category 2 list and whether we would expect the developer to submit an application for approval. As of the date we issued this guidance, however, we have found that the level of risk for all of the products on the list has not changed. We will continue to monitor for any adverse event reports that may indicate any change in product risks.

### **i. IGAs With a History of Safe Use**

FDA does not expect developers to submit applications for approval to market IGAs in food animals that are equivalent to genomic sequences that are found in animals of the same species (recognizing normal biological variability, e.g., variability in sequence of the targeted gene

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<sup>18</sup> For additional information on FDA review expectations, see this [webinar for animal biotechnology developers](#) and this [webinar on Category 2 IGAs](#).

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resulting in the same phenotype and baseline mutations in the genome) with a history of safe use in animal agriculture food production. By “history of safe use in animal agriculture food production,” we mean that the IGA is based on a sequence and a trait found within a conventionally raised species and population of food-producing animals for which there is a history of safe use. We plan to provide additional information that will help developers seeking to demonstrate that their IGA “has a history of safe use in animal agriculture food production.”

### **ii. IGAs Theoretically Achievable Through Conventional Breeding and Resulting in No Change in Food**

FDA also does not expect developers to submit applications or get approval to market IGAs in food animals where (1) the alteration is equivalent to what could be theoretically achieved through conventional breeding; (2) based on the genomic sequence, the alteration is not expected to result in changes to food composition; (3) the intended use of the alteration does not include any effect on animal disease, human disease, or other health outcome; and (4) the alteration has no identified risks of concern to humans, animals, or the environment for the intended use. We consider alterations that “could be achieved through conventional breeding” to exclude insertion of transgenes, but could potentially include deletions, small insertions in coding regions, and possibly deletions, small insertions, and changes to non-coding regions. As with other IGAs that are Category 2 (see below), we expect to evaluate whether these IGAs pose an environmental risk when determining whether we expect submission of an application for approval.

### **iii. Other IGAs That May Be Category 2**

We will evaluate other IGA products in animals to determine whether they fit within Category 2 and, consequentially, we would not expect the developer to open an investigational file or to submit an application for approval. In some cases, there are categories of IGAs that are likely to be Category 2 if the developer can address certain risk factors specific to that category of product. For those categories, we plan to issue separate guidance explaining the particular risk factors we’ll consider when we decide whether specific IGA products in these categories have enough evidence to demonstrate they fit in Category 2 and that we don’t expect developers to submit an application for approval to market these IGAs in animals.

We may expand the categories of IGAs in animals that FDA considers to be potentially Category 2, or reduce or eliminate the data expectations for Category 2 determinations. We will base our decisions on our experience with the type of IGA, available scientific data and information, the type of animal, and our determination of risk.<sup>19</sup>

For other IGA products that are not in a defined category of IGAs covered by a guidance document, on a case-by-case basis we will determine whether the specific IGA fits in Category 2 and we would not expect the developer to open an investigational file or to submit an application

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<sup>19</sup> This regulatory approach is consistent with recommendations within the National Academies of Sciences, Engineering, and Medicine report, “Preparing for Future Products of Biotechnology.” National Academies of Science, Engineering, and Medicine. 2017. Preparing for Future Products of Biotechnology. Washington, DC: National Academies Press (NASEM Report) (<https://nap.nationalacademies.org/catalog/24605/preparing-for-future-products-of-biotechnology>) (Accessed February 16, 2024).

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for approval. In general, here are some questions we plan to consider when making this decision about risk:

- Is there anything about the IGA itself that poses a human, animal, or environmental risk? For example, does it contain sequences that can cause human or animal disease either intrinsically or by recombination?
- For an unintentional environmental release or escape, does the animal with the IGA pose any more of an environmental risk than its counterpart with no IGA?
- Are there concerns over the disposition or disposal of animals with the IGA that could pose human, animal, or environmental risks?
- Are there any other safety questions or risk issues?

For example, after reviewing information about an IGA intended to cause a *Zebra danio* aquarium fish to fluoresce in the dark (GloFish), especially about potential environmental risks related to unintentional release, we decided we didn't expect the developer to submit an approval application to us prior to marketing their product. ([GloFish](#) and *Int'l Ctr. for Tech. Assessment v. Thompson*, 421 F. Supp. 2d 1 (D.D.C. 2006)).

Note that we do plan to take environmental risks into account when making these decisions. FDA has to comply with the environmental review requirements of the National Environmental Policy Act (NEPA) when it takes certain types of actions, e.g., when we establish an investigational exemption (i.e., the sponsor has a valid investigational file) or review and approve an application. But when we do not take an action, like an approval, no NEPA process takes place.<sup>20</sup> Even though NEPA does not apply, we will look at environmental risks when deciding whether we intend to exercise enforcement discretion over a product. Based on the product, species, and conditions of use, among other things, we will look at whether there is any risk of the animal containing the IGA escaping and establishing in the environment and whether anything about the IGA itself or disposal of the animal containing the IGA or its wastes might pose an environmental risk. Information about our environmental review process under NEPA that would also be relevant to environmental review for products that may be eligible for enforcement discretion is available [on our website](#).

If you are a developer and you think your IGA may be eligible for enforcement discretion, contact us (see contact information on the title page of this document). We will help you open a veterinary master file (VMF) (which does not require you to pay [User Fees](#)) to get the process started. Once you open a VMF, we will send you a letter confirming the opening of the file and explaining that, if you are planning to ship your animals to new investigators, you will need to include a shipment notice that you submit to us prior to shipment of the animals. In addition, we also encourage you to consult CVM's [Veterinary Innovation Program \(VIP\)](#) webpage. This

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<sup>20</sup> 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(2)(C). Approval of an application is a major Federal action that triggers the requirement for environmental analysis under NEPA. 40 CFR 1508.18; see 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. Thompson*, 421 F. Supp. 2d 1, 8 (D.D.C. 2006).

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program is intended to assist developers of innovative veterinary products, including certain IGAs in animals, by providing intensive technical and programmatic assistance throughout the FDA review process in order to make it as efficient as possible.

### **iv. USDA Determinations**

For IGAs in animals for food use that are subject to USDA authority as amenable species<sup>21</sup> (21 U.S.C. § 453 et seq., 601 et seq.), developers should work with the slaughter and/or processing establishment(s) to determine if USDA Food Safety and Inspection Service (FSIS) sketch label approval for the finished meat or poultry product is required (9 CFR 412.1). FDA will share information with USDA during the risk-determination process<sup>22</sup> in order to facilitate USDA's determinations but it is the developer's responsibility to ensure that they have obtained any necessary USDA determinations prior to marketing.

### **v. Post FDA Determination**

Once FDA determines that it intends to exercise enforcement discretion over an IGA in an animal, the next step for the developer is to register facilities used in the development of these Category 2 IGAs in animals and list the IGA products if they are commercially marketed. This information helps FDA know which of the IGA products it has evaluated are on the commercial market. See 21 CFR part 207. (Note that if you/the developer or a contract service provider has facilities that are only engaged in standard breeding practices, such as embryo transfer and cloning, we may not expect you or the contract service provider to register those facilities. Contact us if your development plan includes such facilities.) [Registration](#) is a one time, relatively simple, electronic process; however, if you have problems registering, please contact us for help (see first page of guidance for contact information).

If someone intends to breed an animal containing an IGA that FDA has approved or has determined is Category 2 with another animal containing an IGA that FDA has approved or also has determined is Category 2 *or* with an animal that does not contain an IGA and you are making no new claims, then you do not need to request a separate risk determination from FDA and nothing further is required, including any additional product listing.

If you are a farmer, grower, or other entity that just has animals with IGAs that FDA has approved or determined is Category 2 on your farm or other premises, including the offspring of those animals, and you are not the developer of the IGA in the animal or marketing the animals with any new claims, then, as a general matter, you do not have to register or list with FDA and you can engage in your ordinary activities (e.g., breeding, growing, etc.) without contacting FDA.

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<sup>21</sup> Amenable species include cattle, sheep, swine, goats, fish of the order Siluriformes, and poultry (i.e., chickens, turkeys, ducks, geese, guineas, ratites, and squabs).

<sup>22</sup> <https://www.fda.gov/about-fda/domestic-mous/mou-225-24-010>

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### **2. Approval and Post-Approval**

For Category 3 IGAs for which FDA expects to receive an application for pre-market approval, the standards for approval (21 U.S.C. § 360b, 21 CFR part 512) and for NEPA review (42 U.S.C. § 4321 et seq, 40 CFR 1500 et seq, 21 CFR part 25) are set forth in statutes and regulations. However, the type and amount of data required to meet the FD&C Act approval standard and the NEPA review standard may vary based on a product's risks. For example, the environmental risks posed by an animal that could escape and breed in the wild requires submission of more information in an environmental assessment under NEPA than a highly contained animal that produces a human drug (i.e., "biopharm"). Similarly, we will generally require more data to show food safety of animal-derived food that will be marketed for human consumption than for a biopharm animal of a food-producing species that has multiple controls in place to help ensure that it will not enter the food supply. For information on the approval process as it applies to IGAs in animals, see Draft GFI #187B. Also, for information on review timeframes (all application submissions are subject to timeframes for review), see GFI #187B and User Fee Performance Goals.<sup>23</sup> As explained above, as the Agency and the scientific community gain more understanding and experience and the technology becomes more precise, the assessment of potential risks of IGAs in animals may diminish and we may decide that these types of IGAs would fit in Category 2 and, at that time, FDA would not expect developers to submit applications for approval prior to marketing such IGAs in animals.

For information on post-approval requirements for approved IGAs in animals, see Draft GFI #187B. As noted in that draft guidance document, post-approval reporting and recordkeeping responsibilities belong to sponsors and not to farmers or producers who are independent of the sponsor and raise animals that contain IGAs.

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<sup>23</sup> As of the date of this guidance, the performance goals can be found at <https://www.fda.gov/media/116001/download>. Among the most significant timeframes are: For major technical sections of an application, FDA has a 180-day review timeframe from the date of submission. For the administrative application that is submitted after all technical sections are complete, FDA has a 60-day review timeframe from the date of submission; and for investigational food use authorizations, FDA has a 100-day review timeframe from the date of the request for authorization.