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USDA Announces Proposal to Regulate Agricultural Animal Biotechnology

December 23, 2020

Food, Drug, and Device

On December 21, 2020, the United States Department of Agriculture (USDA) released an Advanced Notice of Proposed Rulemaking (ANPR) to seek comment on a contemplated regulatory framework that, if finalized, would transition to USDA portions of the Food and Drug Administration's (FDA's) pre-existing animal biotechnology regulatory oversight.

In particular, USDA proposes to use its existing authorities under the Animal Health Protection Act (AHPA), the Federal Meat Inspection Act (FMIA), and the Poultry Products Inspection Act (PPIA) to provide end-to-end regulatory oversight from pre-market reviews through post-market food safety monitoring for livestock, horses, Siluriformes (including catfish) and poultry that are intended for agricultural purposes and that are modified or developed using genetic engineering. Under this framework, USDA's Animal and Plant Health Inspection Service (APHIS) would conduct a safety assessment to ensure that the covered animals are not more susceptible to or more likely to transmit pests or diseases. The USDA's Food Safety and Inspection Service (FSIS) would conduct a pre-slaughter food safety assessment to ensure that the slaughter and processing of these animals would not result in adulterated products.

This ANPR was developed in response to a June 2019 Executive Order on agricultural biotechnology, which directed federal agencies to modernize the regulatory framework for agricultural biotechnology products.

Background

Under current law, FDA's Center for Veterinary Medicine (CVM) regulates the genetic engineering of animals pursuant to the new animal drug provisions of the Federal Food, Drug, and Cosmetic Act (FDCA). The FDCA defines a new animal drug as "an article (other than food) intended to affect the structure or any function of the body of … animals." Subject to a limited exception,[1] FDA currently takes the position that altered genomic DNA intended to affect the structure or function of an animal meets the definition of an animal drug irrespective of whether the resulting GE animals are intended for food, or to produce pharmaceuticals (or any other

[1] In FDA-CVM, Draft Guidance for Industry (GFI) #236, "Regulation of Mosquito-Related Products," FDA has proposed to clarify that the phrase "articles (other than food) intended to affect the structure or any function of the body of man or other animals" does not include articles intended to prevent, destroy, repel, or mitigate mosquitoes for population control purposes. Instead, such products are pesticides regulated by the Environmental Protection Agency (EPA).

substances).[2] FDA outlines its current approach to regulation of genetic engineering in FDA Guidance for Industry #187, "Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs."

FDA has used this authority to approve genomic alterations in animals for use as food. For example, on December 14, 2020, FDA approved an intentional genomic alteration in a line of domestic pigs, referred to as GalSafe Pigs, which may be used for *both* food or human therapeutics. These GalSafe pigs lack alpha-gal sugar on the surface of their cells, making them safe for use for individuals with Alpha-gal Syndrome (AGS), who may have mild-to severe reactions to the alpha-gal sugar. FDA has also approved such an alteration in AquAdvantage Salmon, a genetically engineered salmon intended for food use.

Key Provisions of the ANPR

The contemplated regulatory framework would apply to "amenable species modified or developed using genetic engineering." The "amenable species" are those animal species subject to the FMIA or PPIA, which laws regulate the way meat and poultry must be produced or sold for human food use. According to the ANPR, such species include cattle, sheep, goats, swine, horses, mules, other equines, fish of the order Siluriformes (which includes catfish), domesticated chickens, turkeys, ducks, geese, guineas, ratites, and squab. The framework would only apply to these species if "intended for agricultural purposes," such as for human or animal food, fiber, and labor. USDA assumes that, for purposes of this regulatory framework, genetic engineering means "techniques that use recombinant, synthesized, or amplified nucleic acids to modify or create a genome" per 7 C.F.R. § 340.3.

USDA proposes to provide coordinated end-to-end regulatory oversight from pre-market animal pest and disease risk to post-market human food safety reviews for those species intended for use as human food. USDA anticipates a two-tiered system of review.

First, USDA anticipates an expedited safety review for "any genetic modification made that is already known to occur in the gene pool of the species, except in cases where an animal health claim is made for the animal or the modification is known to adversely affect animal health." Through a molecular characterization of the modification, the review would verify that "no unintended disruptions of endogenous genes, unintended DNA insertions, or off-target changes" occurred. If USDA determines that the modification made using genetic engineering is equivalent to what can be accomplished through conventional breeding practices, the animal would not be subject to further regulation under the contemplated framework.

Second, for all other types of modifications not eligible for an expedited safety review, USDA would conduct an animal health risk assessment and, if the animal is intended for use as human food, a food safety assessment. Until these assessments are made, a permit would be required for the import, interstate movement, or environmental release of the animal.

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[2] *See* FDA-CVM, Guidance For Industry (GFI) #187 Regulation of Intentionally Altered Genomic DNA in Animals, noting that "[A]ltered genomic DNA" refers to the portion of an animal's genome that has been intentionally altered, available at: https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM113903.pdf

The proposed regulatory framework is intended to operate under a Memorandum of Understanding (MOU) with FDA consistent with each agency's authorities and statutory obligations. According to the ANPR, a MOU would facilitate an orderly transition from FDA to USDA of the oversight of amenable species modified or developed using genetic engineering once the regulatory framework is established. The MOU would also "set clear roles, responsibilities, and timeframes for the interactions between FDA and USDA."

Notable Exemptions

The contemplated regulatory framework would not apply to amenable species modified or developed using genetic engineering intended for non-agricultural purposes, including medical and pharmaceutical purposes and gene therapies. FDA would continue its review of these amenable species, as well as the regulation of dairy products, table and shell eggs, and animal food that are derived from amenable species.

Comment Period

USDA will be accepting comments on the proposed rule for 60 days following its publication in the Federal Register. USDA is particularly seeking public comment on the following questions:

Scope of Regulations and Review

- The contemplated regulatory framework would apply to animals of the "amenable species" (cattle, sheep, goats, swine, horses, mules, other equines, fish of the order Siluriformes, chickens, turkeys, ducks, geese, guineas, ratites, and squabs) modified or developed using genetic engineering that are "intended for agricultural purposes" such as human or animal food, fiber, and labor. What are the agricultural uses for "amenable species" other than use as human or animal food? Should the contemplated regulatory framework define "agricultural purposes other than food"? If so, how should it be defined?
- Is the safety review process described above (see "Contemplated Regulatory Framework") appropriate to protect human health, including for both human consumption and disease transmission? Why or why not?
- Is the safety review process described above (see "Contemplated Regulatory Framework") appropriate to protect livestock health of both the target animal and its herd or flock? Why or why not?
- Are there types of modifications that should make an animal of an amenable species modified or developed using genetic engineering eligible or ineligible for the expedited safety review process outlined above?
- How should USDA define "off-target changes" for the purposes of expedited review of animals in which modifications already known to occur in the gene pool of the species are made without the insertion of DNA?
- Should USDA exempt certain types of genetic modifications of amenable species intended for agricultural use from regulation? If so, what types of modifications and why?
- Which types of genetic modifications should not be exempted from regulation? Why?
- Should any entities or activities be exempt from regulation? If so, what types of entities and why? If not, why not?

- Are there any statutory or regulatory constraints and/or advantages that need to be considered?

Risk Assessment Process

- How should USDA assess risks to animal health? Which pest or disease risks should be considered? Should any other adverse effects (e.g., specific adverse effects on the biology of the animal modified or developed using genetic engineering) be considered? Please be specific and include examples when possible.
- Under what circumstances would a controlled animal safety study be needed versus general surveillance over the health of the herd?
- What information, beyond that described in the "Contemplated Regulatory Framework" section of the document, would USDA need to consider in order to properly review and assess risks associated with amenable species modified or developed using genetic engineering that are intended for agricultural purposes? Are there limitations to the types of information that could be gathered or technologies that could be used to inform the evaluation of animal health claims? If so, please describe the limitations.
- What is the minimal information would need to consider to evaluate animal disease claims made for the animals of the amenable species modified or developed using genetic engineering? What are the limitations of current technologies that exist to evaluate animal disease claims?
- What other animal health claims, aside from disease resistance, should USDA require developers to validate? Why?
- Under the current proposal, USDA is not performing a post-market evaluation of animal health. Should USDA require developers to submit information in order to monitor risks to animal health post-market? Why?
- Are there any gaps in the contemplated framework with respect to animal and human health, and if so, how might they be addressed?

Regulatory Authority and Framework

- Does the contemplated regulatory framework provide adequate scope and flexibility to regulate current and future advances in agricultural animals developed using genetic engineering?
- What, if any, terms related to the regulation of animals of the amenable species modified or developed using genetic engineering would need to be defined under the contemplated regulatory framework?
- Should animals of the amenable species modified or developed using genetic engineering with multiple uses (such as an amenable species modified or developed using genetic engineering and intended for both biomedical/pharmaceutical purposes and agricultural purposes) receive any different treatment than other amenable species during USDA's review processes? What steps should USDA take to ensure efficient review of these products? What steps should USDA take to account for existing regulatory burden when a product must be reviewed both by USDA and by another agency?

- Do you have any other specific concerns or recommendations for appropriately reducing regulatory burdens involving the regulation of amenable species modified or developed using genetic engineering by USDA as described in this document?

Genetic Engineering and Conventional Breeding

- What are the known current limits of conventional breeding in animals in terms of generating and/or selecting for a specific trait, or multiple traits?
- What problems are entities currently attempting to solve using animals modified or developed using genetic engineering?

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With R&D efforts well underway and regulated industry seeking a more streamlined approach to federal oversight in this area, we expect the Biden administration will move forward with engaging stakeholders to consider an updated regulatory framework.

If you have any questions concerning the material discussed in this client alert, please contact the following members of our Food, Drug, and Device Practice Group:

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**District of Columbia bar application pending; supervised by principals of the firm.*