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Sarah Copper

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FOLLOWING THE FRAMEWORK: INTENTIONAL GENOMIC ALTERATIONS IN ANIMALS

Sarah Copper

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Intentional genomic alterations in animals or genetically engineered animals have existed in their modern form since the 1980s. However, the introduction of these animals into our food supply has been a more recent development. The federal government has taken steps in an attempt to regulate these products in a streamlined and efficient manner but has faced criticism in their approach. While the Food and Drug Administration ("FDA") is currently responsible for the regulation of intentional genomic alterations ("IGAs") in animals, there is significant effort behind transferring that oversight to the United States Department of Agriculture ("USDA"). However, in the meantime, there are products currently approved and on the market. These products are facing legal hurdles as well as consumer backlash. This paper will address what intentional genomic alterations in animals are, the framework that established the regulatory structure surrounding these products, the current relevant regulatory guidance, the IGA products currently on the market and the legal issues facing these products.

I. Defining Intentional Genomic Alterations in Animals

The FDA defines animals with intentional genomic alterations as animals whose genomes have been intentionally altered using modern molecular technologies.[1] These technologies can 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.[2] Traditionally, recombinant DNA ("rDNA") technology has been used in plants and animals to create genetic modifications. rDNA techniques involve splicing DNA sequences from various sources and introducing them into animals via techniques that result in random integration events.[3] Animals whose genomes have been intentionally altered by rDNA technology have been produced since the early 1980s when two scientists at the University of Washington, Ralph Brinster and Richard Palmiter, reported on the development of

[1] *See* FOOD & DRUG ADMIN., REGULATION OF INTENTIONALLY ALTERED GENOMIC DNA IN ANIMALS: DRAFT GUIDANCE (2017).
[2] *See id.*
[3] *See id.*

mice altered in this manner.[4] Not long thereafter, Robert Hammer, a scientist at the University of Pennsylvania demonstrated that rDNA techniques could be used to intentionally alter the genomes of rabbits and pigs.[5]

More recently, newer more precise technologies have been developed. Some of these include the use of "nucleases" or "genome editing technologies" including engineered nuclease/nucleotide complexes such as zinc finger nucleases ("ZFN"), transcription activator-like effector nucleases ("TALENs"), and the clustered regulatory interspersed short palindromic repeats ("CRISPR").[6] These nucleases are intended to introduce alterations at specific sites in the genome, rather than the more random changes associated with rDNA technology, resulting in more predictable alterations.[7]

These intentional genetic alterations can be heritable or non-heritable. A heritable genetic alteration will be passed on to the animal's offspring while a non-heritable genetic alteration will not be passed on and is generally used as gene therapy.[8] This distinction between heritable and non-heritable is an important consideration in how FDA currently regulates intentional genomic alterations in animals. All of the product currently approved as food contain heritable intentional genomic alterations.

Some animals with intentional genomic alterations are intended to produce medical products, such as human drugs or medical devices. While the FDA's Center for Veterinary Medicine ("CVM") is responsible for oversight of the IGA in the animal, the products derived from that animal are subject to regulation by other FDA centers such as the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, the Center for Devices and Radiological Health, or the Center for Food Safety and Applied Nutrition.[9]

II. Regulation of IGA in Animals

Animals with intentional genomic alterations are regulated as new animal drugs under section 201 of the Food, Drug, and

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[4] *See* Ralph L. Brinster et al., *Somatic Expression of Herpes Thymidine Kinase in Mice Following Injection of a Fusion Gene into Eggs*, HSS PUB. ACCESS, Nov. 1981 at 223.
[5] *See* Robert E. Hammer et al., *Production of Transgenic Rabbits, Sheep, and Pigs by Microinjection*, 315 NATURE 680 (June 20, 1985).
[6] *See* FOOD & DRUG ADMIN., *supra* note 1.
[7] *See id.*
[8] *See id.*
[9] *See id.*

Cosmetic Act. A "drug" under the relevant section 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 FD&C Act includes "any 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, or that is so recognized but has not been used to a material extent or for a material time." So, the genomic alteration itself is considered the new animal drug because the alteration of the animal's genetic makeup affects the structure or function of the animal. For example, a genomic alteration that enables a fish to grow at a faster rate is regulated as an animal drug. However, arriving at this regulatory framework was not an easy task and continues to be a subject of concern.

III. History of Regulation of Intentional Genomic Alterations in Animals and Interagency Collaboration

In June of 1986, the White House released the Coordinated Framework for the Regulation of Biotechnology. This framework laid out a comprehensive Federal regulatory policy for ensuring the safety of biotechnology products. The framework stated that "the application of traditional genetic modification techniques is relied upon broadly for enhanced characteristics of food (e.g., hybrid corn, selective breeding), manufactured food (e.g., bread, cheese, yogurt), waste disposal (e.g., bacterial sewage treatment), medicine (e.g., vaccines, hormones), pesticides (e.g., Bacillus thuringiensis) and other uses."[10] To ensure the safety of these types of products, Congress charged various Federal agencies with implementing an array of laws.[11] However, recognizing that there might gaps in regulations given the discovery and use of rDNA and cell fusion, the Reagan Administration formed an interagency working group to address the matter.[12] The working group concluded that the current law adequately addressed regulatory needs.[13] However, "For certain microbial products, however, additional regulatory requirements, available under existing statutory authority, needed to be

[10] Coordinated Framework for Regulation of Biotechnology, 51 Fed. Reg 23302 (June 26, 1986).
[11] *See id.*
[12] *See id.*
[13] *See id*.

established."[14] The working group also established that the three primary regulatory agencies responsible for these genetically engineered products were the U.S. Environmental Protection Agency ("EPA"), the Food and Drug Administration ("FDA"), and the U.S. Department of Agriculture ("USDA").[15] The framework was "expected to evolve in accord with the experiences of the industry and the agencies, and, thus, modifications may need to be made through administrative or legislative actions."[16] It described a risk-based, scientifically sound basis for the oversight of activities that introduce biotechnology products into the environment.[17]

This framework was first updated in 1992 to outline the appropriate agencies and authorities for the exercise of authority and oversight under the current regulations.[18] The 1992 update reaffirmed that federal oversight "focuses on the characteristics of the biotechnology product and the environment into which it is being introduced, not the process by which the product is created" and clarified that "[e]xercise of oversight in the scope of discretion afforded by statute should be based on the risk posed by the introduction and should not turn on the fact that [a biotechnology product] has been modified by a particular process or technique."[19] Moreover, the 1992 Update to the Coordinated Framework stated that "[i]n order to ensure that limited federal oversight resources are applied where they will accomplish the greatest net beneficial protection of public health and the environment, oversight will be exercised only where the risk posed by the introduction is unreasonable."[20] The 1992 update likely was spurred by the progress that AquaBounty was making with their genetically engineered salmon that was created to develop an Atlantic salmon that grows faster during the earlier stages of growth.[21] AquaBounty's website states that in 1989 the genetically engineered salmon was created and in 1991 the company was founded to commercialize the innovation.[22]

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[14] *Id.*
[15] U.S. DEP'T OF AGRIC., MODERNIZING THE REGULATORY SYSTEM FOR BIOTECHNOLOGY PRODUCTS (2017), https://usbiotechnologyregulation.mrp.usda.gov/2017_coordinated_framework_update.pdf.
[16] Coordinated Framework for Regulation of Biotechnology § 23303.
[17] 1992 Update to the Coordinated Framework, 57 Fed. Reg. 6663, 6753 (Feb. 27, 1992).
[18] MODERNIZING THE REGULATORY SYSTEM FOR BIOTECHNOLOGY PRODUCTS, s*upra* note 15.
[19] *Id.*
[20] *Id.*
[21] *About Us*, AQUABOUNTY, https://aquabounty.com/about-us (last visited Nov. 28, 2022).
[22] *Id.*

This product was the first genetically engineered animal that was intended for human consumption.

The FDA first released draft guidance on the regulation of genetically engineered animals containing heritable recombinant DNA constructs on September 18, 2008.[23] The document was titled, Guidance for Industry #187 "Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs."[24] The purpose of the draft guidance was to clarify that the new animal drug provisions of the Federal Food, Drug and Cosmetic Act ("FFDCA") applied to the rDNA constructs in genetically engineered animals.[25] This guidance defined genetically engineered animals as "animals modified by recombinant DNA ("rDNA") techniques. The term GE animal can refer to both animals with heritable rDNA constructs and animals with non-heritable rDNA constructs."[26] This guidance laid out important principles regarding FDA oversight and regulation of genetically engineered animals. First, the FDA stated that they would be exercising enforcement discretion with regard to genetically engineered animals of non-food-species that are regulated by other government agencies or entities and genetically engineered animals of non-food-species that are raised and used in contained and controlled conditions.[27] The FDA states that the factors they consider when choosing to exercise enforcement discretion is the potential for human, animal or environmental risk; potential for greater environmental risk than a non-genetically engineered counterpart; human, animal, or environmental concerns over disposition of genetically engineered animal; or other safety questions not adequately addressed by the sponsor.[28] The guidance then goes through the requirements of a new animal drug application, the approval process and post approval requirements.[29]

This first draft guidance was met with a staggering response. There were over 28,000 comments that were mostly statements

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[23] FOOD & DRUG ADMIN., RESPONSE TO PUBLIC COMMENTS ON DRAFT GUIDANCE FOR INDUSTRY #187 (2008).
[24] FOOD & DRUG ADMIN., INTENTIONAL GENOMIC ALTERATIONS (IGAS) IN ANIMALS (2022).
[25] MODERNIZING THE REGULATORY SYSTEM FOR BIOTECHNOLOGY PRODUCTS, *supra* note 15.
[26] FOOD & DRUG ADMIN. CTR. FOR VETERINARY MED., GUIDANCE FOR INDUSTRY 187, REGULATION OF GENETICALLY ENGINEERED ANIMALS CONTAINING HERITABLE RECOMBINANT DNA CONSTRUCTS, (2009).
[27] *Id.*
[28] *Id.*
[29] *Id.*

opposing genetic engineering in animals.[30] However, the substantive comments that the FDA addressed in their response contained concerns, analysis, recommendations, and opinions regarding a variety of topics related to genetic engineering in animals. Some of the important issues raised were the adequacy of the new animal drug application ("NADA") in regulating these products, interagency collaboration, animal health and safety, food safety, food labeling, and environmental safety. Importantly, the FDA's response to the thousands of comments made it clear that they did not intend to promulgate any new regulations regarding genetically engineered animals. The final guidance was published in January of 2009.

The next regulatory update went back to the coordinated framework. The framework was further updated starting in 2015 by the EPA, FDA and USDA at the behest of the Executive Office of the President.[31] The purpose of this update was to clarify the roles and responsibilities of the subject agencies in the regulation of biotechnology products, to develop a long-term strategy that would ensure the federal regulatory system is prepared for future biotechnology products and commission an independent, expert analysis of the future landscape of biotechnology products.[32] Specifically, the memorandum requesting this update established four objectives:

i. clarifying which biotechnology product areas are within the authority and responsibility of each agency;
ii. clarifying the roles that each agency plays for different product areas, particularly for those product areas that fall within the responsibility of multiple agencies, and how those roles relate to each other in the course of a regulatory assessment;
iii. clarifying a standard mechanism for communication and, as appropriate, coordination among agencies, while they perform their respective regulatory functions, and for identifying agency designees responsible for this coordination function; and

[30] *Id.*
[31] MODERNIZING THE REGULATORY SYSTEM FOR BIOTECHNOLOGY PRODUCTS, s*upra* note 15.
[32] *Id.*

> iv. clarifying the mechanism and timeline for regularly reviewing, and updating as appropriate, the Coordinated Framework to minimize delays, support innovation, protect health and the environment and promote the public trust in the regulatory systems for biotechnology products.[33]

In looking specifically at genetic engineering in animals in the update, the FDA addresses "GE Animals" in a separate section.[34] The update details that FDA regulates GE animals under the NADA provisions of the FFDCA. Specifically, the update details that the rDNA construct will be overseen by the Center for Veterinary Medicine ("CVM"), including the safety of any food derived from the GE Animal and the validity of the claims by the sponsor.[35] Essentially, the CVM will ensure that GE Animals are safe for consumption by humans and that they work as intended. The update goes on to detail that GE animals producing substances to be used in or as drugs, biologics, or medical devices for use in humans, FDA's Center for Drug Evaluation and Research ("CDER"), Center for Biologics Evaluation and Research ("CBER"), or Center for Devices and Radiological Health ("CDRH") has responsibility for reviewing those products that are produced by GE animals under their respective purview.[36]

The USDA also claims responsibility for animal health in the update. Under the Animal Health Protection Act ("AHPA"), the Animal and Plant Health Inspection Service ("APHIS") will conduct an animal health risk assessment to determine if the genetically engineered animal poses a risk to livestock.[37] If such a risk is found, the genetically engineered animal would be subject to import or transport restrictions to minimize the risk.[38] This second update to the coordinated framework for the regulation of biotechnology was finalized in 2017.[39]

Also in 2015, the FDA updated the guidance document titled, "GFI #187, Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs." This document was further edited and released for public comment in

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[33] *Id.*
[34] *Id.*
[35] *Id.*
[36] MODERNIZING THE REGULATORY SYSTEM FOR BIOTECHNOLOGY PRODUCTS, *supra* note 15.
[37] *Id.*
[38] *Id.*
[39] *Id.*

2017 under the title "Guidance for Industry #187 Regulation of Intentionally Altered Genomic DNA in Animals." FDA stated that the draft revised Guidance for Industry was being released "to clarify its approach to the regulation of intentionally altered genomic DNA in animals. This guidance addresses animals whose genomes have been intentionally altered 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.[40] At this time, the FDA changed the nomenclature surrounding genetically engineered animals to animals with intentional genomic alterations. This change clarifies the article that is being regulated. The FDA expands on this point, stating:

> *A specific DNA alteration is an article that meets the definition of a new animal drug at each site in the genome where the alteration (insertion, substitution, or deletion) occurs. The specific alteration sequence and the site at which the alteration is located can affect both the health of the animals in the lineage and the level and control of expression of the altered sequence, which influences its effectiveness in that lineage. Therefore, in general, each specific genomic alteration is considered to be a separate new animal drug subject to new animal drug approval requirements.*[41]

The 2017 draft guidance also restated the agency's position on enforcement discretion. However, the 2017 draft guidance has not yet been finalized. This is likely due to the comments received and the continued fight for oversight responsibilities between agencies. Several actions have been taken since the release of this draft guidance to further change the regulatory landscape regarding intentional genomic alterations in animals.

On June 11, 2019, President Trump signed an Executive Order on "Modernizing the Regulatory Framework for Agricultural Biotechnology Products." This Executive Order calls for, among other things, regulatory streamlining in order to facilitate the innovation of agricultural biotechnology to the market efficiently, consistently, and safely under a predictable, consistent, transparent, and science-based regulatory framework.[42] In response to the

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[40] FOOD & DRUG ADMIN. CTR. FOR VETERINARY MED., *supra* note 26.
[41] *Id.* at 7.
[42] U.S. DEP'T OF AGRIC., *Memorandum of Understanding Between the United States Department of Agriculture and the Food and Drug Administration*, DEP'T

objectives laid out in this Executive Order, on December 28, 2020, the USDA issued an advanced notice of proposed rulemaking addressing the possibility of transferring jurisdiction over some genetically engineered animals from FDA to USDA.[43] Following this advanced notice of proposed rulemaking, on January 13, 2021, the USDA and Department of Health and Human Services signed an agreement that the USDA would take over portions of the FDA's oversight of genetic modifications in agricultural animals and biotechnology for agricultural animals.[44] One key aspect of this agreement was the FDA's commitment to "immediately implement a streamlined, risk-based approach to oversight of intentional genomic alterations in animals."[45] The agreement goes to state, "FDA and USDA will work on a communication plan to explain FDA's involvement with agriculture amenable species developed using genetic engineering."[46]

Under this framework, "USDA would safeguard animal and human health by providing end-to-end oversight from pre-market reviews through post-market food safety monitoring for certain farm animals modified or developed using genetic engineering that are intended for human food," a USDA announcement states.[47] The FDA would retain authority over genomic alterations for nonagricultural purposes and over dairy products, eggs, some meat products, and animal feed derived from modified animals.[48] The agreement also states that the FDA would implement a streamlined risk-based approach to oversight of intentional genomic alterations in animals.[49] Previously, the USDA had authority over genetic engineering of plants, while the FDA regulated all genetic engineering of animal species.

The FDA adamantly opposed this transition at the time. Former FDA Commissioner Stephen Hahn voiced some of his concerns regarding the advanced notice of proposed rulemaking via

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OF HEALTH & HUM. SERVS., at 1 (Jan. 13, 2021) https://www.aphis.usda.gov/biotechnology/downloads/mou-usda-fda.pdf.

[43] U.S. DEP'T OF AGRIC., *Secretary Perdue Announces Groundbreaking Proposal to Transfer Agricultural Animal Biotechnology Regulatory Framework to USDA*, (Dec. 21, 2020), https://www.usda.gov/media/press-releases/2020/12/21/secretary-perdue-announces-groundbreaking-proposal-transfer.

[44] *Secretary Perdue Statement on MOU on Animal Biotechnology*, U.S. DEP'T OF AGRIC. (Jan. 19, 2021), https://www.usda.gov/media/press-releases/2021/01/19/secretary-perdue-statement-mou-animal-biotechnology.

[45] *Memorandum of Understanding, supra* note 42.

[46] *Id.*

[47] *Secretary Perdue Statement on MOU on Animal Biotechnology, supra* note 44.

[48] *Id.*

[49] *Id.*

Twitter.[50] Hahn stated that the FDA did not support the MOU and had no intention of abdicating its public health mandate.[51] USDA officials announced March 7 they were reopening the proposal's comment period, which had expired in February of 2021.[52] The agency accepted comments through May 7, 2021.[53] However, no action has been taken as a result of those comments.

However, most recently, on April 14, 2022, eleven agricultural institutions have penned a letter to Secretary Vilsack supporting the agency's advance notice of proposed rulemaking and calling for change in the federal regulation of gene editing in livestock.[54] The letter stated that the current FDA regulatory approach stifles innovation in the livestock sector, citing the decades long regulatory process.[55] The letter states that:

> *Gene editing technology offers livestock producers the opportunity to address the serious sustainability, animal health, and food security challenges facing our food supply in the 21st century. However, this potential can only be achieved if we have federal policies that are risk and science-based, and that permit the meaningful adoption of these products by producers, supply chains, and consumers.*[56]

However, at this time, neither the FDA nor the USDA have come out with any new regulations regarding intentional genomic alterations in animals. Therefore, the controlling regulations are the new animal drug application rules governed by the FDA.

IV. Investigational New Animal Drug Application

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[50] Michael Mezher, *HHS, FDA Dispute Spills Out Onto Twitter*, REGUL. FOCUS (Jan. 19, 2021), https://www.raps.org/news-and-articles/news-articles/2021/1/hhs-fda-dispute-spills-out-onto-twitter.
[51] *Id.*
[52] Steve Davies, *USDA Reopens Comment Period On Animal Biotech Regulatory Overhaul*, AGRIPULSE (Mar. 5, 2021, 12:13 PM), https://www.agri-pulse.com/articles/15457-usda-reopens-comment-period-on-animal-biotech-proposal.
[53] *Id.*
[54] Letter from Nat'l Ass'n of State Dep'ts of Agric. to U.S. Dep't of Agric. Sec'y Tom Vilsack (Apr. 14, 2022), https://www.nasda.org/wp-content/uploads/2022/07/4.14.22_Gene_Editing_Livestock_Letter.01.pdf.
[55] *Id.*
[56] *Id.*

A new animal drug is "deemed unsafe" prior to FDA's approval of said animal drug.[57] Therefore, the regulations surrounding new animal drugs place restrictions on interstate shipment of these products prior to opening an investigational new animal drug file.[58]

During the investigational stage of developing a new intentional genomic alteration, the FDA recommends opening an investigational new animal drug file before shipping the products for any purpose.[59] Commonly these products need to be shipped to and from different laboratories. 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 the FDA.[60] The regulations surrounding investigational new animal drug files specify labeling and record-keeping requirements, animal disposition, and conditions under which food from animals used for clinical investigations can be introduced into the food supply.[61] The FDA recommends a disposition plan for these investigational products as they want to ensure that these products do not enter the market before they are approved.[62] If a sponsor wishes to introduce investigational animals or animal products into the food supply, they must request an Investigational Food Use Authorization.[63] Actions on investigational new animal drug applications are considered major federal actions under the National Environmental Policy Act ("NEPA"), and as such may require preparation of an environmental assessment ("EA") and a finding of no significant impact ("FONSI") or an environmental impact statement ("EIS").[64]

V. Low Risk Products

FDA has stated that for products that are low risk, the Agency may not expect developers to seek approval of these intentional genomic alterations. The FDA will conduct a risk-based review to determine if a product is low risk. If the review finds the

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[57] MODERNIZING THE REGULATORY SYSTEM FOR BIOTECHNOLOGY PRODUCTS, *supra* note 15.
[58] 21 C.F.R § 511.1 (2022).
[59] MODERNIZING THE REGULATORY SYSTEM FOR BIOTECHNOLOGY PRODUCTS, *supra* note 15.
[60] 21 CFR § 511.1 (2022).
[61] MODERNIZING THE REGULATORY SYSTEM FOR BIOTECHNOLOGY PRODUCTS, *supra* note 15.
[62] *See* 21 C.F.R. § 511.1(b)(5) (2022).
[63] *Id.*
[64] 21 C.F.R. § 511.1(b)(10) (2022); 21 C.F.R. § 25.15 (2022); 21 C.F.R. § 25.22 (2022).

intentional genomic alteration to be low risk, the FDA will not require developers to seek approval for the alteration.[65] FDA will publish a summary of their risk-based review to increase transparency into the approval process. [66] There is currently only one intentional genomic alteration approved for use in animals intended for food use, the PRLR-SLICK cattle. The alteration found in this cow is intended to create a short slick haircoat allowing for greater heat tolerance.[67] Review for low-risk alterations includes a review of molecular characterization, phenotypic data and animal safety, human food safety and environmental risk.

VI. Intentional Genomic Alterations in Animals Review Process

The FDA's draft guidance establishes a recommended process for completing the pre-approval assessments for intentional genomic alterations. The first three steps focus on the establishing and characterizing the altered genomic DNA in the resulting animals, specifically: product identification; the molecular characterization of the altered genomic DNA; and the molecular characterization of the lineage of animals whose genomes have been intentionally altered.[68]

The product identification or definition encompasses the specific lineage of animals whose genomes have been intentionally altered, that is, the altered genomic DNA as well as the animals containing it, and the purpose of the altered genomic DNA that is the subject of the new animal drug application.[69]

The molecular characterization of the altered genomic DNA serves to describe the components and composition of the product. The FDA recommends that a sponsor provides information for identifying and characterizing the altered genomic DNA that will be introduced into the progenitor of the animal to be marketed. – this is the first step in the hazard identification component of the safety review of the new animal drug application.

The molecular characterization of the lineage of animals whose genomes have been altered serves as the second part of the

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[65] U.S. DEP'T OF AGRIC., *Intentional Genomic Alterations (IGAs) in Animals: Low Risk IGAs*, (Jun. 1, 2022), https://www.fda.gov/animal-veterinary/intentional-genomic-alterations-igas-animals/intentional-genomic-alterations-igas-animals-low-risk-igas.
[66] *Id.*
[67] FOOD & DRUG ADMIN., RISK ASSESSMENT SUMMARY – V-006378 PRLR-SLICK CATTLE 1.
[68] *Id.*
[69] *Id.*

hazard identification by continuing the analysis of the intentionally altered genomic DNA and the location of the genomic alteration in the resulting animal as well as the production of the animal(s) intended to be used in commerce and any potential hazards that may be introduced into those animals as part of their production.

Information gathered in the following steps helps establish whether the genomic alteration poses any risks to humans, the health of the animal or the environment. In the phenotypic characterization of animals whose genomes have been intentionally altered, the FDA is looking for data regarding the target animal safety requirements and whether the genomic alteration or its expression product cause any direct or indirect toxicity.

As part of the genotypic and phenotypic durability assessment, FDA requires information to ensure that the altered genomic DNA in the animal resulting from the specific alteration event is durable. There is a reasonable expectation that the altered genomic DNA is stably inherited, and the phenotype is consistent and predictable. This would include developing a sampling plan.

As part of the food safety and environmental safety assessment, the sponsor must look at direct and indirect toxicity including allergenicity, via food consumption of the intentional genomic alteration in the animal and the potential for indirect toxicity or unintended food consumption hazards. For the environmental safety assessment, most applications for animals whose genomes have been intentionally altered would have to be evaluated to determine whether such an approval will individually or cumulatively result in significant environmental impact.

Lastly, for effectiveness and claim validation, the sponsor must show the they have validated the claims for the characteristics that the animals whose genomes have been intentionally altered are intended to exhibit. For example, in the case of animals whose genomes have been intentionally altered that are intended to resist disease, the sponsor should demonstrate that those animals are indeed resistant to that disease.

Again, each genomic alteration is an individual new animal drug, that is each specific genomic alteration is considered to be a separate new animal drug subject to new animal drug approval requirements.[70] If a sponsor wishes to introduce multiple genomic alterations resulting in one final animal lineage, the FDA

[70] REGULATION OF INTENTIONALLY ALTERED GENOMIC DNA IN ANIMALS: DRAFT GUIDANCE, *supra* note 1.

recommends that the sponsor contact the agency to discuss regulatory options and the kinds of scientific questions that would have to be addressed in an application.[71] In the research phase, an Investigational new animal drug file may be created to research several different types of alterations. [72] Each new animal drug approval covers all animals containing the same genomic alteration derived from the same alteration event.[73] Animals containing the genomic alteration as a result of breeding between an intentionally altered animal and its non-intentionally altered counterpart animal are covered by the new animal drug approval.[74]

VII. Products currently approved for human consumption by FDA

A. AquAdvantage Salmon

AquAdvantage Salmon contains an intentional genomic alteration that causes the salmon to grow at a rapid rate.[75] AquAdvantage Salmon was developed by the company AquaBounty in 1989.[76] The heritable intentional genomic alteration was introduced to the parent stock of fish and continually bred to create the AquAdvantage school that is being harvested today.[77] According to the FDA, AquAdvantage is able to grow at a faster rate than conventional salmon because "it contains an rDNA construct that is composed of the growth hormone gene from Chinook salmon under the control of a promoter, which is a sequence of DNA that turns on the expression of a gene, from ocean pout."[78] These salmon grow twice as fast as wild salmon, reaching eight to twelve pounds within 18 months instead of thirty-six months.[79] AquaBounty has facilities in Canada, Panama, and two facilities in the US, one currently in

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[71] *Id.*
[72] *Id.* at 7-8
[73] *Id.* at 8.
[74] *Id.*
[75] *AquAdvantage Salmon Fact Sheet*, FOOD & DRUG ADMIN. (April 28, 2022), https://www.fda.gov/animal-veterinary/aquadvantage-salmon/aquadvantage-salmon-fact-sheet.
[76] AQUABOUNTY, *supra* note 21.
[77] *Our Salmon*, AQUABOUNTY, https://aquabounty.com/our-salmon (last visited Nov. 28, 2022).
[78] *AquAdvantage Salmon Fact Sheet supra* note 75.
[79] Casey Smith, *First shipments of genetically modified salmon go to restaurants in eastern U.S.*, ACHORAGE DAILY NEWS, June 1, 2021, https://www.adn.com/business-economy/2021/06/01/genetically-modified-salmon-head-to-restaurants-in-eastern-us/.

operation in Indiana and the other potentially in Kentucky.[80] All of the AquaBounty facilities are enclosed and on land in an effort to mitigate the risk of AquAdvantage escaping into the ocean.[81]

AquAdvantage has been approved by the FDA as food for human consumption. The FDA states "the salmon are safe to eat, the introduced DNA is safe for the fish itself, and the salmon meet the sponsor's claim about faster growth."[82] However, this product has faced significant opposition from consumers. Consumer groups have pressured major retailers from selling AquAdvantage in their stores.[83] AquAdvantage was first harvested for sale in May of 2021.[84] However, because of the consumer response, the product is only available in select restaurants.[85]

B. GalSafe Pig

In December of 2020, the FDA approved a first of its kind intentionally altered genomic line of domestic pigs which may be used for human food or human therapeutics.[86] The pigs were originally created to potentially provide a source of porcine-based materials to produce human medical products that are free of detectable alpha-gal sugar.[87] The FDA states that as an example, "GalSafe pigs could potentially be used as a source of medical products, such as the blood-thinning drug heparin, free of detectable alpha-gal sugar. Tissues and organs from GalSafe pigs could potentially address the issue of immune rejection in patients receiving xenotransplants, as alpha-gal sugar is believed to be a cause of rejection in patients."[88]

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[80] *Our Farms,* AQUABOUNTY, https://aquabounty.com/our-farms (last visited Dec. 2, 2022).
[81] *AquAdvantage Salmon Fact Sheet supra* note 75.
[82] *Id.*
[83] Dan Flynn, *AquaBounty salmon is what's for dinner if you can find it*, FOOD SAFETY NEWS (Sept. 4, 2020), https://www.foodsafetynews.com/2020/09/aquabounty-salmon-is-whats-for-dinner-if-you-can-find-it/.
[84] Smith, *supra* note 79.
[85] *Id.*
[86] FOOD & DRUG ADMIN., *FDA Approves First-of-its- Kind Intentional Genomic Alteration in Line of Domestic Pigs for Both Human Food, Potential Therapeutic Uses,* FDA NEWS RELEASES, (Dec. 14, 2020), https://www.fda.gov/news-events/press-announcements/fda-approves-first-its-kind-intentional-genomic-alteration-line-domestic-pigs-both-human-food#:~:text=Today%2C%20the%20U.S.%20Food%20and,for%20food%20or%20human%20therapeutics (last visited Nov. 29, 2022).
[87] *Id.*
[88] *Id.*

In determining that the meat from the GalSafe pigs is safe for human consumption, the FDA not only looked at the safety of the intentional genomic alteration, but also at the product developer's intention to market the product for its ability to eliminate alpha-gal sugar on pigs' cells.[89] The FDA determined that food from GalSafe pigs is safe for human consumption. The FDA also focused on ensuring the effectiveness of the intentional genomic alteration through the evaluation of data demonstrating that there is no detectable level of alpha-gal sugar across multiple generations of GalSafe pigs.[90] The FDA found no greater environmental risk, or antimicrobial resistance risk than is found with conventional pigs.[91] However, the product developer's new animal drug application did not include data regarding food allergies, the FDA's review process did not evaluate food safety specific to allergies related to alpha-gal sugar.[92] Anecdotally, the meat resulting from the intentional genomic alteration found in the GalSafe pigs is safe for individuals who suffer from alpha-gal syndrome, an allergy to alpha-gal sugar that is spread through lone star tick bites.[93] While GalSafe pigs are approved by the FDA for human consumption, they have not yet been approved for their biomedical uses.[94] Once approved, the intentional genomic alteration could produce organs that are viable for human transplant. So far, doctors have transplanted a kidney and a heart from these pigs to humans under special authorizations from FDA.[95]

C. PRLR-SLICK Cattle

Approved as a low-risk intentional genomic alteration, the PRLR-SLICK cattle have been altered to present with a short, slick haircoat.[96] The cattle with the IGA are referred to as PRLRSLICK cattle. This heritable intentional genomic alteration was introduced using a genome editing technique known as CRISPR in two

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[89] *Id.*
[90] *Id.*
[91] *Id.*
[92] *FDA Approves First-of-its- Kind Intentional Genomic Alteration in Line of Domestic Pigs for Both Human Food, Potential Therapeutic Uses supra* note 86.
[93] Chris Clayton, *FDA Approves Biotech Swine: Pigs Become First Genetically Altered Animals Approved for Food, Medical Use in US*, PROGRESSIVE FARMER (Dec. 21, 2020, 7:58 AM CST), https://www.dtnpf.com/agriculture/web/ag/livestock/article/2020/12/14/pigs-become-first-genetically-food.
[94] *Id.*
[95] Roni Caryn Rabin, *Patient in Groundbreaking Heart Transplant Dies*, N.Y. TIMES (Mar. 9, 2022), https://www.nytimes.com/2022/03/09/health/heart-transplant-pig-bennett.html.
[96] RISK ASSESSMENT SUMMARY – V-006378 PRLR-SLICK CATTLE, *supra* note 67.

"founder" beef calves.[97] Because this alteration is heritable, it is can be passed on to offspring, only requiring introduction to the parent stock, similar to the AquAdvantage salmon.[98] The PRLR-SLICK alteration is equivalent to a naturally occurring mutation that occur in several breeds of conventionally raised cattle that have adapted to warmer climates.[99] The FDA's risk assessment summary states "the slick mutations confer a short, 'slick' haircoat, and cattle with the slick phenotype have been reported to be better at withstanding hot weather."[100]

Acceligen, the company sponsoring the application for the PRLR SLICK cattle, submitted genomic data and other information to FDA to demonstrate that the intentional genomic alteration present is genetically equivalent to naturally occurring mutations with a history of food safety.[101] Essentially, the data provided shows that the genetic pattern created by the intentional genomic alteration has been present in food used for human consumption safely.

These three products all present different goals by producers: faster growing proteins; food products aimed at solving allergen issues and being used in medical products, and lastly a product addressing animal welfare concerns and allowing for cattle ranching in harsher weather climates. These products all have very different goals, are part of different industries and therefore require different considerations in how they should be regulated. The types of issues these products are facing now are only going to compound as technologies advance and more diverse products are brought to market.

VIII. Regulatory Hurdles facing IGA in Animals - Labeling

Animals containing intentional genomic alterations are subject to the Bioengineered Foods Disclosure Standard. This standard was created by the USDA and is administered through the Agricultural Marketing Service ("AMS").[102] Prior to the Bioengineered Foods Disclosure Standard, the FDA had released

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[97] *Id.*
[98] *Id.*
[99] *Id.*
[100] *Id.*
[101] RISK ASSESSMENT SUMMARY – V-006378 PRLR-SLICK CATTLE, *supra* note 67.
[102] U.S. DEP'T. OF AGRIC. MARKETING SERVICE, *Agricultural Mktg. Serv.* https://www.ams.usda.gov/rules-regulations/be (last visited Dec. 1, 2022).

guidance that did not require labeling on genetically engineered salmon because it was not materially different from other Atlantic Salmon and met the regulatory standard for Atlantic Salmon.[103] The FDA supported voluntary labeling of non-genetically engineered products while cautioning against deceptive mislabeling products. For comparison, the FDA's approach to labeling this genetically engineered salmon was similar to their approach to labeling for Genetically Modified Organisms.

Again, when looking specifically at genetically engineered salmon, as a result of FDA's decision regarding voluntary labeling, language was added to the 2016 federal budget requiring labeling for genetically engineered Atlantic salmon before it could be imported into the United States.[104] This back and forth on the labeling requirements caused many issues for AquaBounty, as its grow out facility was located in Indiana while their salmon eggs were cultivated in Canada.[105] The import alert blocked AquaBounty from bringing its eggs to the Indiana facility for growing.[106]

In December of 2018, the USDA passed the National Bioengineered Food Disclosure Standard.[107] This USDA-developed standard regulates the labeling of foods that are genetically engineered. According to the National Bioengineered Food Disclosure Standard, a bioengineered food, "contain[s] detectable genetic material that has been modified through certain lab techniques and cannot be created through conventional breeding or found in nature."[108] USDA maintains the List of Bioengineered Foods which includes AquAdvantage Atlantic salmon.[109] Therefore, products that contain AquAdvantage must be appropriately labeled under the National Bioengineered Food Disclosure Standard as

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[103] FOOD & DRUG ADMIN., *Draft Guidance for Industry: Voluntary Labeling Indicating Whether Food Has or Has Not Been Derived From Genetically Engineered Atlantic Salmon* (March 2019), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/draft-guidance-industry-voluntary-labeling-indicating-whether-food-has-or-has-not-been-derived.

[104] Christine Blank, *New Labeling Rule Paves Way for GM Salmon to Enter US Market* (December 21, 2018), https://www.seafoodsource.com/news/supply-trade/new-labeling-rule-paves-way-for-gm-salmon-to-enter-us-market.

[105] *Id.*

[106] *Id.*

[107] U.S. DEP'T OF AGRIC., *BE Disclosure*, https://www.ams.usda.gov/rules-regulations/be (last visited Dec. 1, 2022).

[108] *Id.*

[109] Scott Gottlieb, *Statement from FDA Commissioner Scott Gottlieb, M.D., on Continued Efforts to Advance Safe Biotechnology Innovations, and the Deactivation of an Import Alert on Genetically Engineered Salmon* (April 8, 2019), https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-continued-efforts-advance-safe-biotechnology.

bioengineered with one of the four disclosure options: on-package text stating "bioengineered food"; the USDA approved symbol for bioengineered food; an electronic or digital link, such as a QR code; or a text message disclosure prompt.[110] Once the National Bioengineered Food Disclosure Standard was enacted, the labeling requirement for genetically engineered salmon was met and the import alert was lifted.[111] This legislative effort was spearheaded by Alaska Senator Lisa Murkowski in an effort to protect the salmon industry in Alaska.[112] However, even though FDA now refers to these products as intentional genomic alterations in animals, they are still subject to the National Bioengineered Food Disclosure Standard.

IX. Legal Hurdles – NEPA lawsuit

AquAdvantage has been in development and in the market for over thirty years. Given this presence and novelty as the first entrant into this market, it has faced greater scrutiny from consumer and advocacy groups. Most notably, the Institute for Fisheries Resources commenced an action against the FDA relating to the environmental analysis the agency conducting in reviewing AquaBounty's new animal drug application for AquAdvantage. The case challenged FDA's authority to regulate the altered salmon and questioned the agency's decision to regulate the salmon as a drug instead of a food.[113] The court found that FDA did have the authority to regulate genetically engineered salmon to avoid a regulatory gap and ensure proper oversight of the food derived from the animal.[114] However, the environmental claims warranted greater consideration.

As part of the FDA's analysis of AquAdvantage, they conducted an environmental review under the National Environmental Policy Act ("NEPA").[115] At the time of this review,

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[110] U.S. DEP'T OF AGRIC. AGRIC. MKTG. SERV., NATIONAL BIOENGINEERED FOOD DISCLOSURE STANDARD, 2 (2019).
[111] Statement from FDA Commissioner Scott Gottlieb, M.D., on continued efforts to advance safe biotechnology innovations, and the deactivation of an import alert on genetically engineered salmon, FOOD & DRUG ADMIN., April 08, 2019, https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-continued-efforts-advance-safe-biotechnology.
[112] Press Release, Lisa Murkowski Campaign for U.S. Senator, *Murkowski Statement on New U.S. Genetically Engineered Salmon Facility*, (May 1, 2018), https://www.murkowski.senate.gov/press/release/murkowski-statement-on-new-us-genetically-engineered-salmon-facility-.
[113] Brigit Rollins, *Fish Fumbles: GE Salmon Faces Uncertainty*, THE NAT'L AGRIC. LAW CTR. (Feb. 5, 2020), https://nationalaglawcenter.org/fish-fumbles-ge-salmon-faces-uncertainty/.
[114] *Id.*
[115] *Id.*

AquaBounty was only utilizing facilities in Canada and Panama at the time it applied to FDA.[116] The company's United States based facilities were not yet operational. Therefore, the agency only conducted an environmental review on the foreign facilities when making its decision to approve AquAdvantage.[117] FDA conducted the environmental assessment as required by NEPA and made a finding of no significant impact.[118] That is, FDA determined that AquAdvantage posed no environmental or ecological risks due to the containment measures in place at the facilities in Canada and Panama. As a result, no further assessment was needed by either Fish and Wildlife Service (FWS) or National Marine Fisheries Service (NMFS).

The plaintiffs challenge both of FDA's conclusions.[119] They alleged that FDA violated federal law by failing to conduct an appropriate review under either NEPA or the Endangered Species Act (ESA).[120] First, the plaintiffs aver that by only drafting an Environmental Impact Statement, FDA violated NEPA's provisions regarding the environmental assessment.[121] Second, the plaintiffs argued by not conferring with FWS or NMFS regarding potential harms to endangered wild salmon, FDA was in further violation of the ESA.[122]

In deciding the motion for summary judgment, the court stated that because the FDA did not conduct an analysis of "what might happen to normal salmon in the event the engineered salmon did survive and establish themselves in the wild," the FDA had violated NEPA and the ESA in approving the original application for the AquAdvantage facilities in Canada and Panama.[123] The case was "remanded to the FDA without vacatur for reconsideration of the environmental assessment under NEPA and the ESA analysis."[124] Therefore, the opinion orders the FDA to reanalyze the possible

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[116] *Id.*
[117] *Id.*
[118] *Q&A on FDA's Approval of AquAdvantage Salmon*, FOOD & DRUG ADMIN., https://www.fda.gov/animal-veterinary/aquadvantage-salmon/qa-fdas-approval-aquadvantage-salmon (last visited Dec. 2, 2022).
[119] Rollins, *supra* note 113.
[120] *Id.*
[121] Plaintiffs' Motion For Summary Judgment at 1, Inst. for Fisheries Res. v. Hanh, Case No. 3:16-cv-01574-VC (N.D. Cal. May 13, 2020).
[122] *Id.*
[123] Order Granting in Part and Denying in Part Plaintiffs' Motion for Summary Judgment at 16, Inst. for Fisheries Res. v. U.S. Food & Drug Admin., Case No. 16-cv-01574-VC (N.D. Cal. Nov. 5, 2020).
[124] *Id.*

escape by the salmon that are then able to survive and thrive in the wild.

However, the court order does not revoke the approval of AquAdvantage and the facilities in Canada, Panama, and Indiana that are currently in place. In fact, in response to the court's order, AquaBounty CEO, Sylvia Wulf stated in a statement, "The focus of this decision was on the potential environmental impacts, and the judge confirmed the 'low' threat to the environment of our salmon . . . [t]his decision will not have an impact on our on-going operations on Prince Edward Island, Canada to produce eggs or in the raising and selling of AquAdvantage salmon from our farm in (Albany) Indiana. We are committed to working with FDA on next steps and continue to evaluate the legal decision."[125] As a result, AquAdvantage was made available in May of 2021 at select restaurants.[126] Again there has been more pushback from advocacy groups including the Center for Food Safety regarding AquaBounty's compliance with the court's order. In March of 2022 the Center filed a Freedom of Information Act Lawsuit against the FDA for unlawfully withholding records regarding FDA's environmental assessment of genetically engineered (GE) salmon and a planned Ohio-based production facility.[127]

X. Conclusion

The regulatory and overall legal landscape surrounding animals with intentional genomic alterations or genetically engineered animals is complex and evolving rapidly. While the ultimate goal is to ensure the safety of the animals subjected to the alteration, the food or biomedical products produced from that animal, and the environment, it is clear that no one can agree on how to achieve that safety. This is exemplified by the agencies' difficulty in determining what to call these products – IGAs in animals, GE

[125] Sam Hill, *Federal judge rules FDA must reevaluate effects of potential GE salmon escape*, SEAFOOD SOURCE (Nov. 9, 2020), https://www.seafoodsource.com/news/food-safety-health/federal-judge-rules-fda-must-reevaluate-effects-of-potential-ge-salmon-escape.
[126] Smith, *supra* note 79.
[127] *FDA Sued Over Failure to Release Documents Regarding Approval of Genetically Engineered Salmon, Planned Ohio Production Facility*, CTR. FOR FOOD SAFETY (Mar. 10, 2020), https://www.centerforfoodsafety.org/press-releases/6589/fda-sued-over-failure-to-release-documents-regarding-approval-of-genetically-engineered-salmon-planned-ohio-production-facility.

animals, bioengineered animals, or something different. In order to adequately regulate these products and ensure safety, a unified regulatory structure surrounding these products needs to be developed.