Biotechnology Innovation Organization

February 26, 2021

Docket No. APHIS-2020-0079
Regulatory Analysis and Development, PPD, APHIS, Station 3A-03.8
4700 River Road, Unit 118
Riverdale, MD 20737-1238

Submitted Electronically via Federal eRulemaking Portal (http://www.regulations.gov)

Re: Docket No. APHIS-2020-0079. Regulation of the Movement of Animals Modified or Developed Through Genetic Engineering

Dear Sir or Madam:

The Biotechnology Innovation Organization (BIO) submits these comments in response to the U.S. Department of Agriculture's (USDA's) advance notice of proposed rulemaking and request for public comment on a proposed framework for oversight of certain animals modified or developed through genetic engineering.[1] In particular, USDA proposes a new regulatory framework for amenable species intended for agricultural use, to be administered jointly by USDA's Animal and Plant Health Inspection Service (APHIS) and the Food Safety Inspection Service (FSIS).

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers, and related organizations across the United States and in more than 30 other nations. BIO's members operate at the intersection of biology and technology to cure patients, protect our climate, and nourish humanity. As BIO looks to the future, we seek to advance disruptive innovation by 1) being a voice of science and for science; 2) uniting and empowering biotech innovators and their ecosystem to improve lives; 3) removing barriers to innovation; 4) championing broad access to biotech breakthroughs and scientific equality; and 5) catalyzing resilient and sustainable biobased economies. BIO's member companies represent some of the global leaders in the use of biotechnology in animals.

The use of biotechnology to improve the genetics of animals used in agriculture has the potential to address a broad array of important societal issues—improvements in animal health and welfare; improved human health and nutrition; responding effectively to zoonotic disease; adaptation to climate change; and increasing the sustainability of animal agricultural production. The success of these innovations is critically dependent on regulatory systems that ensure animal health and welfare, food safety, and protection of the environment, but does so in a way that does not disincentivize development and commercialization of innovation. Without an efficient and effective system for

[1] 85 Fed. Reg. 84269-84275 (December 28, 2020).

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oversight of animal biotechnology, the U.S. risks its leadership role in utilizing important, cutting-edge tools to address these critical societal challenges.

The U.S. Food and Drug Administration (FDA) currently regulates the safety of animals containing "intentional genomic alterations" utilizing the new animal drug authority of the Federal Food, Drug, and Cosmetics Act (FFDCA), as described in draft "Guidance for Industry #187" (GFI 187).[2] For reasons discussed in more detail below, BIO has long expressed concern over FDA's approach to oversight of animal biotechnology, the implementation of which is having real and immediate impacts on our members and the U.S.'s ability to remain the leader in animal biotechnology.

We appreciate USDA's leadership in proposing an alternative approach to oversight of biotechnology in animals intended to address some of the concerns expressed by BIO and other animal biotechnology stakeholders. We remain committed to continuing to work collaboratively with USDA, FDA, and other Executive Branch offices on the urgent need to develop a regulatory system for products of animal biotechnology that continues to ensure the safety of the animals, consumers, and the environment while fostering innovation and expedited commercialization of beneficial improvements to agricultural animals.

Our comments are organized into the following sections: 1) outline of general "good governance" principles for effective regulatory oversight, with an outline of BIO's policy goals for oversight of animal biotechnology; 2) critical review of FDA's current system of oversight; 3) comments on the regulatory framework proposed by USDA; and 4) issues to consider related to the transition of oversight from FDA to USDA.

For clarification, our comments herein relating to USDA's proposal are limited to those specific applications of animal biotechnology intended for agricultural use. Our comments on that proposal should not be interpreted to suggest that USDA adopt oversight of non-agricultural, non-food applications of biotechnology in animals (e.g., ornamental fish, pharmaceutical production, models of human disease, xenotransplantation) or animal species other than those proposed to be subject to USDA jurisdiction under the proposed framework.

I. PRINCIPLES OF EFFECTIVE OVERSIGHT OF ANIMAL BIOTECHNOLOGY

A number of Executive Orders, Agency memoranda, and other Executive Branch directives and materials across multiple Administrations establish best practices and guiding principles for effective rulemaking and regulation. Some of these are specific to oversight of biotechnology and other innovative technologies applicable to agriculture. We briefly describe some of these directives here for providing a broader context to our feedback on USDA's proposal.

The oversight of products derived from biotechnology in the United States was first established by the U.S. White House Office of Science and Technology Policy (OSTP) in 1986, with the publication of the "Coordinated Framework," which established how Federal agencies would exercise oversight of products of the then-emerging technology.[3] OSTP then reiterated those foundational principles in 1992

[2] https://www.fda.gov/media/74614/download
[3] 51 Fed. Reg. 23352-23366 (June 26, 1986).

when it published a memorandum outlining "fundamental scope principles" to aid Coordinated Framework agencies in determining the scope of regulation:

1) A determination to exercise oversight within the scope of discretion afforded by statute should not turn on the fact that an organism has been modified by a particular process or technique, because such a fact is not alone a sufficient indication of risk.

2) A determination to exercise oversight in the scope of discretion afforded by statute should be based on evidence that the risk presented by introduction of an organism in a particular environment used for a particular type of application is unreasonable.

3) Organisms with new phenotypic traits(s) conferring no greater risk to the target environment than the parental organisms should be subject to a level of oversight no greater than that associated with unmodified organisms.[4]

In 2015, the White House directed Coordinated Framework agencies to modernize the regulatory framework for oversight of biotechnology.[5] Accordingly, OSTP published a national strategy to modernize the framework in 2016,[6] followed by an updated Coordinated Framework in 2017.[7] More recently, in 2019, the White House issued an executive order[8] directing the agencies to further review their respective regulatory systems in an effort to streamline processes and remove regulatory barriers that restrict societal access to beneficial innovations. All these recent updates have consistently reaffirmed the Coordinated Framework's foundational principles dating back to 1986 and 1992.

The original Coordinated Framework and its recent modernization build upon a foundation established by many earlier Executive Orders across multiple Administrations directing agencies to follow important principles and requirements in rulemaking.[9] In 2011, the White House published a memorandum to the heads of executive departments and agencies, describing guiding principles for regulation of emerging technologies in particular.[10] These rulemaking principles are aimed at ensuring that regulations are:

- Protective of health and the environment while promoting innovation.
- Based on the best available scientific and technical information.
- Cost-effective and commensurate with risk.
- Flexible and adaptable to accommodate new evidence and learning.
- Simple, clear, transparent, and minimize uncertainty.
- Adopted through a public and transparent process.
- Coordinated with other federal agencies, state authorities, a broad array of stakeholders, and the international community.

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[4] 57 Fed. Reg. 6753-6762 (February 27, 1992).
[5] https://www.epa.gov/sites/production/files/2016-12/documents/modernizing_the_reg_system_for_biotech_products_memo_final.pdf
[6] https://usbiotechnologyregulation.mrp.usda.gov/biotech_national_strategy_final.pdf
[7] https://usbiotechnologyregulation.mrp.usda.gov/2017_coordinated_framework_update.pdf
[8] E.O. 13874.
[9] E.O. 12866, E.O. 13258, E.O. 13422, E.O. 13563, E.O. 13497, E.O. 13610.
[10] https://obamawhitehouse.archives.gov/sites/default/files/omb/inforeg/for-agencies/Principles-for-Regulation-and-Oversight-of-Emerging-Technologies-new.pdf

We believe strongly that government policy regarding the products of biotechnology should be based upon these core "good governance" principles.

In addition to these over-arching governance principles, BIO has four policy goals particular to any regulatory framework for the oversight of biotech animals intended for agricultural use:

1) Oversight must protect animal health and welfare, ensure the safety of food and feed derived from the animals, and consider the possible impacts of the animals on the environment.

2) Implementation of oversight must be clear, transparent, efficient, predictable, timely, and based upon the best available science.

3) Risk assessment must be proportionate to the actual risk posed by the specific species/trait combination. Lower-risk, more-familiar traits, including traits that impart health benefits to humans and animals, should be given a more expedited review than traits for which there is less familiarity or greater uncertainty.

4) Once all appropriate safety reviews are completed, the approved animals should be allowed to be treated as any other farm animal in production and commerce. Ongoing post-market regulatory requirements imposed on such animals, even after they have been determined to be as safe as conventional animals, strongly disincentivizes development and commercialization of farm animals with improved traits.

Additionally, BIO strongly believes that innovation flourishes when science and consumer values are aligned and complement one another. The U.S. government's regulatory approach toward innovative products cannot exist in isolation. It should be supported by credible transparency measures. A proactive approach to transparency stands to build trust and foster an inclusive environment to address our most pressing societal, nutritional, and environmental concerns. BIO encourages the U.S. government to ensure its regulatory policies are durable and legally defensible, based on science and risk, and to articulate to the public its rationale for regulatory approaches. BIO and its members will prioritize an inclusive and impactful approach to transparency, as outlined on BIO's *Growing Trust in Innovation* website.[11]

In the sections which follow, we discuss how the current FDA regulatory framework and the new one proposed by USDA each measure up against these principles of good governance and BIO's stated policy goals.

II. FDA OVERSIGHT OF ANIMAL BIOTECHNOLOGY

At least since the finalization of the first iteration of GFI 187 in 2009, FDA has overseen the safety of certain applications of animal biotechnology by exercising authority over heritable recombinant DNA constructs as "new animal drugs" within the meaning of the FFDCA. In early 2017, FDA proposed revisions to GFI 187, clarifying that its interpretation of the FFDCA authority included all "intentional

[11] https://www.bio.org/growing-trust-innovation

genomic alterations" in animals.[12] FDA's proposed guidance was and continues to be widely criticized by developers, producer groups, academics, and policy organizations, for reasons described more fully below.[13] Despite the criticism, FDA has been operating under the draft guidance since 2017, without revision to address stakeholder concerns.[14] Only two food animal products have been approved by FDA, AquaBounty's AquAdvantage salmon[15] and Revivicor's GalSafe pigs[16], both of which took well over a decade for completion of data package, review and approval.

BIO does not question FDA's FFDCA authority to oversee the safety of animal biotechnology, as was recently upheld in court.[17] However, FDA's insistence on applying to living animals and/or the farms where they are produced regulatory requirements and procedures that are normally applied to conventional veterinary drugs leads to a regulatory system incompatible with the realities of animal agricultural production systems, and comes across as confusing, illogical, and a strong deterrent for research, development, and adoption of new and innovative products.[18]

- According to the guidance document, altered DNA in the animal is considered to be a "drug" regulated by FDA; the founder animal and all subsequent progeny animals are considered to contain "drugs" regulated by FDA; developers receive approval for a New Animal Drug Application.

- Animal developers and producers may have ongoing responsibilities such as "registration and listing of approved founder animals, recordkeeping, filing supplements, and periodic reporting"; requirements to "maintain SOPs for other producers used in the husbandry of these animals (e.g., resulting in biological containment)"; and requirements for "adverse event reporting."

- Labels are required to accompany the animals, including a description of the drug, the animal into which the drug is introduced, and the intended use of the animal containing the drug, in some cases "throughout all stages of its life cycle."

- Imported meat products derived from animals approved in other countries may be considered adulterated and subject to drug residue testing.

As applied, FDA's approach unnecessarily stigmatizes genetically altered animals and their progeny, significantly reducing the likelihood that such animals will be grown by producers or products derived from them accepted by consumers. Under the current FDA system, there is no clear path in which a genetically altered animal may be treated as any other animal intended for agricultural use, even after all appropriate animal health and food safety reviews have been cleared.

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[12] https://www.fda.gov/media/74614/download
[13] https://www.regulations.gov/document?D=FDA-2008-D-0394-0279
[14] In 2020, FDA launched the "Veterinary Innovation Program (VIP)," which established more flexibility in how developers may interact with the agency but made little substantive changes to agency reviews. See: https://www.fda.gov/animal-veterinary/animals-intentional-genomic-alterations/vip-veterinary-innovation-program
[15] https://www.fda.gov/media/93801/download
[16] https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/10168
[17] *Institute for Fisheries Resources v. Hahn*, 424 F. Supp. 3d 740, 751 (N. D. Cal. 2019).
[18] https://www.fda.gov/media/74614/download

We also note that with human gene therapies reviewed by FDA under the authority of the FFDCA, FDA considers the *treatment* to be the drug, not the resulting *genetic changes* induced in a patient receiving the treatment. For example, FDA recently approved a gene therapy product to treat a retinal dystrophy.[19] In this case, the "drug" is the treatment injected into the retina, not the resulting genetic changes induced in retinal cells. If FDA were to review the *treatments* that result in genetic changes in animals (i.e., the animal is the patient, not the drug), FDA would still have adequate oversight of intentional genomic alterations in animals but could do so in a way that could address some (but not all) of the aforementioned issues with its current model of oversight.

In addition to the complications created by the application of the new animal drug framework, the FDA process for reviewing animals with altered DNA is unnecessarily complex and has opaque and highly variable information requirements and timelines that are difficult for developers to navigate. The complexity of the FDA review process may also be compounded by the overlay of the Animal Drug User Fee Act (ADUFA),[20] a periodic amendment to the FFDCA defining developer fees, review timelines, and some procedural steps for review of new animal drugs. While ADUFA provides developers some certainty about timelines for individual steps within the review process, ADUFA does impose some procedural constraints on the agency's animal drug reviews and is also in need of significant modernization. In general, uncertainty and lack of transparency at FDA results in developers not knowing what is expected of them, what the review process entails, or how long the process will take — even *during* product reviews — creating a significant damper on investment in innovation.

Finally, FDA's oversight of genomic alterations in animals makes no meaningful distinctions among applications posing different levels of risk. While the agency uses its enforcement discretion for certain limited categories of gene altered animals (e.g., non-food species regulated by other agencies, or intended only for research purposes, ornamental fish species and a few other limited exceptions), the vast majority of genetic modifications in animals intended for food use are essentially treated the same, regardless of actual risk. Animals with completely novel genetic modifications are regulated with the same level of oversight as animals bearing gene alterations identical to safe, familiar genetic variants already widely present in animal breeds, meat and dairy products of which are consumed daily by millions of Americans. Even those categories of modifications to which FDA applies enforcement discretion are exposed to significant regulatory burdens, which in some cases have increased substantially over time, and without any basis in risk to justify the escalating burden on developers.

In short, FDA's regulatory system as currently implemented falls significantly short of meeting many of the good governance principles outlined above, is disproportionate to the actual risks proposed by the genetic alterations, unnecessarily stigmatizes animals with genetic improvements, and strongly disincentivizes research, development, adoption, and commercialization of animal biotechnology.

III. BIO COMMENTS ON USDA'S PROPOSED REGULATORY FRAMEWORK

USDA is proposing a new regulatory framework for certain animals with genetic alterations intended for agricultural use, to be administered jointly by APHIS and FSIS. Under the proposed system, APHIS

[19] https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/luxturna
[20] https://www.fda.gov/industry/fda-user-fee-programs/animal-drug-user-fee-act-adufa

would use its authority under the Animal Health Protection Act (AHPA) to assess risks to animal health and the health of the national herd, while FSIS would use its meat and poultry inspection authorities under the Federal Meat Inspection Act (FMIA) and the Poultry Products Inspection Act (PPIA) to evaluate the food safety of meat and poultry products derived from the animals. USDA proposes that the FDA would use its enforcement discretion to allow USDA to be the lead agency for oversight of animals intended for agricultural purposes within the scope of the proposal, while other animals with genetic alterations would continue to be overseen by FDA under the new animal drug framework.

Scope of Proposed Framework and Animal Health Risk Assessment

USDA is proposing a regulatory framework for certain genetically engineered animals intended for agricultural uses which provides oversight analogous to a range of issues currently reviewed by FDA (animal, food, and environmental safety), but that does so in a way that it intends to be more streamlined and straightforward. By building a framework based on authorities more appropriate for overseeing animal health, the agency posits that it can create a more intuitive system that avoids many of the round-peg-in-a-square-hole complications resulting from regulating modified animals as if they contained "drugs." The proposal also creates a much clearer path to commercialization, providing a means by which animals can be treated the same as non-GE farm animals once appropriate regulatory reviews are completed and cleared. Additionally, USDA proposes that the framework could result in greater transparency to consumers and other interested stakeholders about products that are under review at USDA than would currently be provided by FDA.

BIO agrees that it is appropriate to oversee the safety of animals intended for agricultural purposes as a distinct category, because genetic modifications in such animals are likely to pose much lower risks than modifications intended for other purposes (cf. pharmaceutical and medical applications) or modifications in non-domesticated species, and because of the distinct ways in which they are intended to be produced and placed in commerce. We note, however, that USDA has chosen to limit its proposed framework to only those "amenable species"[21] subject to the FSIS authorities, rather than the much broader authority granted by the AHPA. The AHPA grants USDA the authority to consider the health of all "farm-raised animals." USDA does not explain why it has elected to limit the exercise of its animal health authority to only the animals subject to its meat and poultry inspection authorities.

We are encouraged by the agency's suggestion that the animal health component of the framework would closely mirror APHIS's updated regulatory framework for genetically engineered plants (7 CFR Part 340).[22] This would give the agency the ability to assess a similar range of issues currently assessed by FDA, but to have much greater flexibility to create categories for expedited review of lower-risk animals and a clearer path for commercialization. We also believe that it is entirely appropriate for USDA to assess any special claims related to animal health; most developers would likely prefer and benefit from an independent validation of such claims, and such an assessment would be analogous to the evaluation of "efficacy" currently assessed by FDA. We would request that such an assessment consider both primary and secondary (derived) benefits of the trait, such as improved sustainability, reduced antibiotic use, improved nitrogen uptake, reduced phosphorous output, etc.

[21] Cattle, sheep, goats, swine, horses, mules, or other equines, fish of the order Siluriformes, domesticated chickens, turkeys, ducks, geese, guineas, ratites, and squabs.
[22] 85 Fed. Reg. 29790-29838 (May 18, 2020).

While the agency does not articulate how it intends to implement the requirements of the National Environmental Policy Act (NEPA), we assume its implementation would be similar to its implementation for genetically engineered plants under 7 CFR Part 340. If so, NEPA implementation in combination with the proposed regulatory system would be expected to provide appropriate analysis of potential impacts on the environment.

Expedited Reviews for Certain Applications of Animal Biotechnology

USDA's proposal requests comment on the possibility of developing expedited reviews and/or exemptions for certain categories of lower-risk genetically engineered animals. BIO strongly supports the adoption of expedited review categories and incorporation of mechanisms to adopt future categories— this is a key feature insufficiently incorporated into FDA's current regulatory system and an important tool in future-proofing a regulatory system as scientific knowledge evolves. One such category could include expedited review of animals containing genetic traits that could have been found in nature or otherwise developed through conventional animal breeding programs. BIO also supports expedited review of genetic modifications in additional breeds of the same species once an initial modification undergoes the full review and is approved— a system analogous to "extensions" for plants available under the previous iteration of 7 CFR Part 340. Developers would also benefit from an expedited review for animals with minimal food safety concerns so research progeny can be cleared for food use even before a single event is selected for commerce.

We note however that BIO does *not* support outright *exemption* from pre-market review for categories of genetically altered animals at this time. Although BIO does strongly support such exemptions for certain categories of GE *plants*, we do not feel that regulatory agencies yet have sufficient experience to establish such categories for animals, nor is the marketplace likely to accept products of animal biotechnology that have not undergone appropriate pre-market review.

Consideration of Food and Feed Safety

USDA's proposed regulatory framework includes two parallel reviews: an animal health review conducted by APHIS under its AHPA authority and a separate food safety-related review conducted by FSIS under the FMIA and PPIA. The proposal is unclear, however, about how the work of the two sub-agencies would relate to each other and be coordinated. Presumably, implementation of the proposed framework would require separate regulations, information requirements, staff, appropriations, etc. for APHIS and FSIS., Implementation would also require careful coordination between the two sub-agencies in order for USDA to truly function as a "one stop shop" (as opposed to two independently functioning regulatory bodies). In order for this aspect of USDA's proposal to function smoothly, USDA should elaborate how it envisions the two functions to be coordinated, preferably with a single point of entry for developers, joint information requirements, and simultaneous, coordinated review.

Although we do not take issue with USDA's interpretation of its inspection authorities as applied to meat and poultry products derived from gene altered animals, we believe that it is not insignificant that those authorities are limited to meat and meat products only; FDA retains authority under the FFDCA to oversee the safety of eggs, dairy, animal feed, and all other non-meat food products not expressly assigned to USDA under the FMIA and PPIA. It is our understanding that most, if not all, animals used in agricultural production will have at least some derivatives subject to both the FSIS authorities and the FFDCA. It is unlikely that any developer would commercialize a product of animal biotechnology for which some, but not all, parts of the animal have been reviewed for food and feed safety.

The food and feed safety aspects of the FFDCA are administered by FDA's Center for Food Safety and Applied Nutrition (CFSAN) and the Center for Veterinary Medicine (CVM), respectively. USDA's proposal would thus potentially result in three different sub-agencies (FSIS, CFSAN, and CVM) having some role in the review of food and feed safety— *in addition to APHIS' animal health review*— significantly increasing the complexity of food and feed safety reviews compared to the current one stop regulatory system offered by FDA/CVM. USDA's proposal does not address how the three agencies would work together to evaluate food and feed safety. Ideally, food and feed safety should be completed as a single, joint review, with a single point of entry, submission package, review process, and regulatory approval, rather than three largely redundant ones working independently and in parallel. The complexities associated with oversight of food and feed safety underscore the need for USDA and FDA to work collaboratively to develop a clearer "coordinated framework" for appropriately risk-based and efficient reviews of the food and feed safety of the use of biotechnology in animals; how the agencies agree to resolve these complexities will be a key determinant in how functional USDA's proposed framework is likely to be.

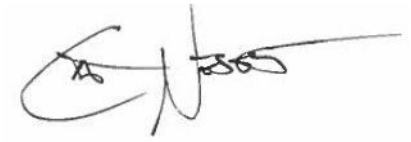
IV. TRANSITION TO NEW REGULATORY FRAMEWORK

If USDA were to adopt the proposed regulatory framework, careful consideration must be given to the treatment of animal products that have either already been approved via the new animal drug system by FDA or are in review by FDA at the time a new framework is implemented. The proposal is unclear as to whether animal products would be required to be reviewed under the new USDA system or if developers would elect to do so voluntarily. Developers of products already approved by FDA may wish have their products approved under the new USDA system, but would likely strongly oppose any requirement to restart an entirely new review at USDA. Similarly, developers with products currently in review at FDA that transition to the USDA system would not want to lose progress gained in FDA reviews or be forced to repeat experimental studies already developed or reviewed by FDA or experience other delays or inefficiencies. Developers in such situations would incur significant, burdensome costs if regulatory studies must be redesigned or repeated due to even small differences between FDA and USDA expectations. If such a regulatory framework were adopted, we would strongly recommend the development of some form of mutual recognition between USDA and FDA, so that approvals already granted by FDA can be recognized by USDA, and regulatory data provided to FDA could be recognized by USDA so that developers do not lose their significant investment in time and research in the transition.

BIO wishes to thank USDA for its leadership in proposing a new regulatory framework for oversight of animal biotechnology intended to address many of the concerns expressed by BIO, its members, and many other stakeholders. We note, however, that successful development and implementation of such a new framework will be critically dependent upon an ongoing constructive and collaborative working relationship between USDA and FDA. We look forward to working with USDA, FDA, OSTP, and other relevant White House Executive Offices to address the urgent need to develop and implement an improved framework for oversight of animal biotechnology that ensures the safety of the animals, consumers, and the environment while fostering innovation and commercialization of beneficial improvements to agricultural animals.

Thank you for the opportunity to provide comments on this draft proposal. Please feel free to contact me directly if you have any questions about our comments.

Sincerely,



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