BREAKTHROUGH INSTITUTE

July 31, 2024

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via regulations.gov

RE: Comments on Draft Guidance for Industry #187B "Heritable Intentional Genomic Alterations in Animals: The Approval Process", 89 FR 35834, Docket No. FDA-2019-D-2648

Dear Dr. Adam Moyer,

The Breakthrough Institute (BTI) appreciates the opportunity to comment on the Food and Drug Administration's Draft Guidance for Industry #187B "Heritable Intentional Genomic Alterations in Animals: The Approval Process" (henceforth "Draft Guidance 187B"). BTI is an independent 501(c)(3) global research center that identifies and promotes technological solutions to environmental and human development challenges. BTI's Food and Agriculture program researches and advocates for policies and strategies to improve productivity growth and reduce the carbon footprint and other environmental impacts of agriculture.

New gene editing technologies can aid in the development and proliferation of genetic traits with beneficial effects. These include improving animal welfare (e.g., polled cattle), enhancing climate resiliency of the food supply (SLICK cattle), reducing the cost and environmental impact of protein production (pigs that excrete less phosphorus, fish with faster growth rates), and bolstering resistance to diseases such as porcine reproductive and respiratory syndrome virus and African swine fever, which threaten livestock health, welfare, and productivity.[1]

As we detail below, Draft Guidance 187B is an important step in creating a clear, consistent, and attainable path to regulatory approval for food animals with intentional genomic alterations (IGAs). We commend the FDA for clarifying potential points of confusion left by the previous draft

[1] For further discussion of genomic alterations in animals that are currently in development or have been approved in certain countries, see Hallerman, E.M., Bredlau, J.P., Camargo, L.S.A. et al. *Towards progressive regulatory approaches for agricultural applications of animal biotechnology.* Transgenic Res 31, 167–199 (2022). https://doi.org/10.1007/s11248-021-00294-3; For a deeper discussion of disease resistant pigs, see Yuan H, Yang L, Zhang Y, Xiao W, Wang Z, Tang X, Ouyang H, Pang D. *Current Status of Genetically Modified Pigs That Are Resistant to Virus Infection*. Viruses. 2022 Feb 17;14(2):417. doi: 10.3390/v14020417. PMID: 35216010; PMCID: PMC8874825.

guidance,[2] offering useful resources to help applicants navigate aspects of the New Animal Drug Application (NADA) process that are not clearly applicable to the review of IGAs in animals, and generally streamlining the application process. These changes reflect the FDA's incorporation of lessons learned in regulating products of novel technologies and its willingness to adapt flexibly.

However, FDA should further clarify the application review process, which remains opaque. This opacity discourages investment in IGAs that may have clear benefits, and may slow the approval process, especially if the number of applications increases.

Ultimately, the FDA is stretching a regulatory process to cover technology that it was not designed for. IGAs in animals, including livestock intended for food use, should be considered separately from new animal drugs. In developing any application and review process for such IGAs, FDA should begin with a framework for identifying potential risks or hazards that is based on the nature and intent of the alterations made, rather than the technology used. Not all IGAs inherently pose a hazard, including some that are novel and would fall under Category 3 in FDA's proposed framework. On the other hand, for example, if the developer is claiming to eliminate an allergen which, if not universally eliminated in all offspring, may expose consumers to a medical risk, then a thorough review of evidence demonstrating product safety beyond a first generation would be applicable. Following this determination, the FDA should consider IGAs within their own application process and regulatory structure based on the nature of the IGA and associated risks.

Respectfully submitted,
The Breakthrough Institute

[2] For the purposes of this comment, we compare draft guidance 187B to Draft Guidance for Industry #187: Regulation of Intentionally Altered Genomic DNA in Animals https://www.federalregister.gov/d/2017-00839

A Step in the Right Direction

We commend the FDA for clearly defining situations where their oversight is not applicable. The draft guidance states that surrogate animals, which do not have IGAs themselves but carry offspring with IGAs, are not covered under food use and disposal regulations for animals with IGAs (section III.C.). This reflects an understanding that there is no evidence that genetic alterations may be transferred from an embryo or fetus to a surrogate animal.

The draft guidance also exempts farmers, ranchers, and other producers who are not engaged in the development of new IGAs, from post approval responsibilities, including registering facilities and animals with the FDA, keeping detailed records of experience with IGAs in animals, and making annual reports to FDA (section V.). Additionally, labeling paperwork requirements have been relaxed: now labeling must only accompany shipments of animals between farmers, ranchers, and other producers if the labeling contains animal care or safety information. The guidance states that labeling is not mandatory when animals are transported between facilities under common ownership or to slaughter facilities (section IV.B.3.). Together, these changes put producers who choose to raise IGA animals on even ground with producers who raise conventional animals, making the development of a market for animals with IGAs far more realistic.

In the new draft guidance, the FDA clears up certain points of confusion which had previously amounted to roadblocks in the approval process. For most new animal drugs, the FDA determines a safe tolerance, or maximum residue level that may be found in final food products. The previous draft guidance offered no explanation of how this approval requirement applied to IGAs in animals. Section IV.B.7. of the revised draft guidance clarifies that FDA's determination of whether an IGA is safe for consumption presupposes that "anything formed in or on the food as a result of the IGA is safe." Therefore there is no concentration that could be considered unsafe, meaning determination of a tolerance is unnecessary.

In addition to these changes, which remove unnecessary burdens and redundancies, Draft Guidance 187B streamlines the approval process by expanding the Veterinary Innovation Program (VIP) to cover new IGA applications (section IV.A.). The Animal Drug User Fee Act establishes a time frame for review of new animal drug applications; however, applicants are required to restart from square one if the information they have provided is found to be insufficient. It is beneficial that FDA can now pause the clock for sponsors that participate in the VIP program if their applications contain remediable mistakes such as insufficient data, and review will continue where it was paused if the sponsor remedies the omission.

Perhaps more important, Draft Guidance 187B states that the Center for Veterinary Medicine (CVM) may consider multiple IGAs or a single IGA in multiple lines or breeds of animals under a single application (section II.). This is a significant step forward from the previous approach, which considered each IGA as an individual animal drug, presumably requiring separate applications. This change may facilitate the approval of animals with multiple IGAs for different phenotypes[3], or multiple complementary IGAs that together create a desired phenotype.

Taken in tandem with the provision that the regulated article is the IGA and not the animal, we hope that the FDA will permit developers to introduce an approved IGA into animals of different breeds from those evaluated during the initial application. When the FDA reviewed the safety of PRLR-SLICK cattle for human consumption, it made a low-risk determination for only two founder animals and their descendants.[4] As a result, the developer is restricted to further promulgation of the SLICK trait through conventional breeding of the founder animals and their offspring. We urge FDA to allow developers to introduce an approved IGA into other animals of the same breed or different breeds; this will enable developers to respond to market conditions and to increase the genetic diversity of animals with an IGA.

Moving Toward a Transparent and Consistent Review Process

While we commend the above changes which update the approval process to be more efficient and approachable, we believe that additional modifications could improve the approval process and FDA's general approach to IGAs in food animals.

At several points, the draft guidance suggests that sponsors of IGAs contact CVM for case-by-case guidance on questions, such as what data they are expected to provide or whether FDA may waive certain application requirements. This flexibility is understandable and may often be necessary given the likelihood of unforeseen scenarios in a novel process. However, the frequency with which the draft guidance resorts to suggesting sponsors contact CVM creates a process that is, on the whole, difficult for developers to understand or prepare for. This makes it challenging for developers of IGAs to accurately budget the time and money needed to complete the review process, therefore deterring investment. In addition, if the pace of application submissions to the FDA increases, as it has for USDA Biotechnology Regulatory Services following implementation of

[3] For example, Argentina approved cattle simultaneously presenting both polled and SLICK genes, while the United States has only approved the SLICK gene (Hallerman et. al., 2022).
[4] FDA Risk Assessment Summary – V-006378 PRLR-SLICK cattle. (03/04/2022) https://www.fda.gov/media/155706/download

the SECURE rule[5], a high level of consultation with the FDA throughout the regulatory process could become untenable for the agency, slowing the timeframe for decision making and further hindering innovation. We suggest that, where possible, the guidance provide more detail on what information sponsors should expect to produce and prepare for application review, including detailing contingent requirements or alternative application pathways.

Many of the roadblocks in the FDA's previous Draft Guidance 187 that have not been corrected in Draft Guidance 187B seem to stem from the NADA process being "unfit for purpose" when applied to IGAs, as Van Eenennaam et al. argued about the previous draft guidance.[6] Ultimately, the Breakthrough Institute would like to see an approval process for IGAs that is separate from the NADA process. The changes we have discussed, while positive, reflect fundamental challenges in stretching a regulatory framework to cover technology that it was not designed for. However, we understand that FDA is working within the powers granted to the agency by Congress, and a full overhaul of the process may require legislative action. Our remaining suggestions are general principles we believe could be applied to further updates of the current process or to the development of a new and separate process.

The Breakthrough Institute believes that the review process for IGAs in animals should be risk based, with approval requirements applying only to alterations with significant risk of resulting in negative impacts including those on animal welfare, or through production of allergens or pharmaceutically bioactive compounds. For instance, alterations intended to increase an animal's muscling may be reviewed for impacts on animal welfare. Eriksson et al. (2018) consider the possibility of proliferating across other breeds a gene found in Belgian blue cattle which results in increased production of high value cuts..[7] The risks associated with this gene include increased incidence of dystocia, infertility, and calf fatalities. While the animal welfare impacts of these unwanted side effects must be taken seriously, it should also be noted that the same effects arose from the initial development of this trait through conventional breeding, and these concerns have discouraged many farmers from raising the breed.

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[5] US Department of Agriculture Animal and Plant Health Inspection Service. *Biotechnology Regulatory Services Annual Stakeholder Meeting*. (2023) https://www.aphis.usda.gov/sites/default/files/2023-stakeholder-meeting.pdf

[6] Van Eenennaam, Alison L. De Figueiredo Silva, Felipe. Trott, Josephine F. Zilberman, David. *Genetic Engineering of Livestock: The Opportunity Cost of Regulatory Delay*. Annual Review of Animal Biosciences 9, P 453-478. (2021) https://doi.org/10.1146/annurev-animal-061220-023052

[7] This specific double muscling gene may be considered a "Category 2" IGA, pursuant to the FDA's Guidance for Industry #187A, in which case the regulatory process discussed in Draft Guidance #187B would not apply. However, we still find it useful as an illustrative example of unintended animal welfare consequences. Eriksson S, Jonas E, Rydhmer L, Röcklinsberg H. *Invited review: Breeding and ethical perspectives on genetically modified and genome edited cattle.* J Dairy Sci. 2018 Jan;101(1):1-17. doi: 10.3168/jds.2017-12962. Epub 2017 Nov 6. PMID: 29102147.

In contrast to pre-market regulation of IGAs, undesirable outcomes from conventional breeding are only restricted by the decisions of producers and consumers. When abnormal problems arise in the development of IGAs in animals, developers typically filter for animals that express the desired traits without the negative side effects. The intended outcomes of genetic engineering are most often to improve animal health and welfare or to achieve economically desirable outcomes, such as increased growth rates without carrying over unwanted traits, something that can be difficult, expensive, and time consuming with conventional breeding.

In addition, the review process should recognize that breeders, farmers and ranchers have no incentive to raise animals with IGAs that may negatively impact animal health. Doing so would risk reducing farmer and rancher productivity and profitability just as adopting conventionally bred animals with known health risks would. The FDA should also consider the costs imposed by a slow review process in delaying the realization of any positive impacts from deployment of IGAs in animals. While ensuring animal and human safety is critical, the FDA should not exclusively consider the negative risks that IGAs in animals pose. Many IGAs in animals will benefit producers, animals, consumers, and the environment. In finalizing its guidance, the FDA should consider how to reduce the likelihood that such benefits will be unnecessarily delayed or unrealized due to the review and approval process.

Finally, while we recognize that the public may be less comfortable with genetic alterations in animals than in crops, the risk of uncontrolled genetic spill-over is fundamentally lower in beef and dairy production, and low in swine and chicken operations as well. Concerns related to the escape or unintentional and uncontrolled spread of animals carrying IGAs should be considered in the context of the species in which the alteration is made and husbandry methods on farms and ranches that may raise offspring with IGAs. The reproduction of livestock is carefully managed in most modern operations and, apart from open-water aquaculture, the likelihood of mating between farm-raised animals and wild populations is vanishingly small.

Livestock production requires significantly more land and other resources per unit of food produced than crops, emits potent greenhouse gasses including methane, and creates conditions for transmission of diseases such as swine and avian flu, among other concerns about air and water pollution and animal welfare. Meanwhile, global demand for meat, eggs, and dairy products are only rising. There is enormous potential benefit from IGAs that may increase the efficiency and climate resiliency of livestock animals, slow the spread of diseases, and eliminate the need for painful practices such as dehorning. It is vital to get the regulatory process for these new technologies right.