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February 26, 2021

By Electronic Submission

(Docket #: APHIS- 2020-0079)

Re: **Comments on USDA Advanced Notice of Proposed Rulemaking for the Regulation of the Movement of Animals Modified or Developed by Genetic Engineering**

The Center for Science in the Public Interest (CSPI)[1], Consumer Federation of America[2], Environmental Defense Fund[3], and National Wildlife Federation[4] appreciate the opportunity to comment on the Advanced Notice of Proposed Rulemaking for the Regulation of the Movement of Animals Modified or Developed by Genetic Engineering (ANPR) issued by United States Department of Agriculture (USDA) (85 FR 84269-75, December 28, 2020). The agency is proposing to regulate certain genetically engineered (GE) food animals that may present a pest or disease risk to livestock under the Animal Health Protection Act (AHPA) and proposing to use its authority under the Federal Meat Inspection Act (FMIA) and the Poultry Products Inspection Act (PPIA) to ensure that meat or poultry from those GE food animals is safe, wholesome, unadulterated, and properly labeled and packaged. The ANPR further states that the proposed regulatory framework would apply to both food and agricultural applications of the GE food animals regulated under either FMIA or PPIA,[5] and would replace the Food and Drug

[1] CSPI is a nonprofit education and advocacy organization that focuses on improving the safety and nutritional quality of our food supply. CSPI seeks to promote health through educating the public about nutrition; it represents citizens' interests before legislative, regulatory, and judicial bodies; and it works to ensure advances in science are used for the public good. CSPI is supported by the over 400,000 member-subscribers to its *Nutrition Action Healthletter* and by foundation grants. CSPI receives no funding from industry or the federal government.

[2] The Consumer Federation of America (CFA) is an association of non-profit consumer organizations that was established in 1968 to advance the consumer interest through research, advocacy, and education. Today, more than 250 of these groups participate in the federation and govern it through their representatives on the organization's Board of Directors.

[3] Environmental Defense Fund (EDF), with over 2.5 million members, is an international non-partisan, non-profit organization dedicated to protecting human health and the environment by effectively applying science, economics, and the law.

[4] The National Wildlife Federation is America's oldest and largest conservation organization, made up of 52 state and territorial affiliates and representing more than 6 million members and supporters across the nation. NWF's mission is to unite all Americans to ensure wildlife thrive in a rapidly changing world.

[5] The ANPR states that USDA would provide regulatory oversight of the following GE food animals: cattle, sheep, goats, swine, horses, mules, other equines, fish of the order of Siluriformes, domesticated chickens, turkeys, ducks, geese, guineas, ratites, and squabs. They would regulate those GE animals not only for human or animal food but also for agricultural purposes (e.g., fiber or labor). For the remainder of this comment, we refer to types of GE animals that USDA would regulate as "GE food animals."

Administration's (FDA) current oversight of intentionally altered genomic DNA in those animals[6] under the "new animal drug" approval process set forth in the Federal Food Drug and Cosmetic Act (FFDCA).

While the current federal regulatory system that places primary responsibility to ensure the safety of GE animals with FDA has both advantages and disadvantages, FDA's oversight has ensured that those animals' welfare is not compromised and that food from those animals is safe for human consumption before entering the market. The ANPR proposes the wholesale substitution of FDA's regulatory oversight with a USDA regulatory system involving three statutes and two different agencies, the Animal and Plant Health Inspection Service (APHIS) and the Food Safety and Inspection Service (FSIS). Both FDA and USDA have some legal authority, expertise, and knowledge to regulate different issues involving GE food animals. For example, FDA is best suited to conduct the molecular level food safety risk assessment of GE animals under the FFDCA while USDA has pre-market legal authority to require proper label claims for those animals under FMIA and PPIA. We believe that both agencies should work together to make sure products are safe and comply with all applicable federal laws before they go to market. However, we do not support the wholesale substitution of USDA oversight for FDA oversight if the goal is to move oversight to a more industry-friendly agency which will reduce regulation without scientific justification (which has been the stated objective of some industry stakeholders advocating for this regulatory change).[7]

Any USDA regulatory system for GE animals must establish oversight that is comparable with FDA's current oversight in its ability to ensure animal and human health and safety. It is impossible to determine whether USDA would (or could) establish such a system due to the lack of detail in the ANPR. In addition, numerous statements in the ANPR suggest that at least some GE animals would receive significantly less oversight than they currently receive under FDA, which could result in the intentional release of animals with risks—both to consumers and the animals themselves--that have not been adequately managed. Therefore, we recommend that USDA (and FDA) consider the following comments before moving forward with the regulatory system outlined in the ANPR.

I. The Federal Government Needs a Science-Based Pre-Market Review and Approval Process that Ensures the Human and Animal Safety of All GE Animals Either at FDA or USDA

[6] FDA's Guidance 187 applies to "intentionally altered genomic DNA in animals." The FDA Guidance states that "Altered genomic DNA may result from 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." The ANPR states that it applies to animals modified or developed by "genetic engineering," which is defined as ''techniques that use recombinant, synthesized, or amplified nucleic acids to modify or create a genome.'' The FDA and USDA definition of terms seem to encompass virtually all the same genetic changes in animals. This document will use the term "genetic engineering" or "GE" since that is the term used in the ANPR.

[7] See for example the testimony of Dr. Michael Paustian, President of the Iowa Pork Producers Association during the U.S. Senate Agriculture Committee hearing on March 12, 2020 (Hearing | Hearings | The United States Senate Committee On Agriculture, Nutrition & Forestry)

The FDA's current regulatory system provides a mandatory pre-market approval process for all GE animals which assesses: (1) the safety of the altered DNA to the animal; (2) the safety of food and feed made from that animal; and (3) the efficacy of the genomic alteration at achieving the desired trait(s). As previously mentioned, FDA's system has succeeded at ensuring the safety of GE animals before entering the market. The ANPR does not explain why FDA's regulatory system should be replaced with USDA oversight under the AHPA, FMIA and PPIA. Neither the ANPR nor any other federal government documents suggest that FDA's system is inadequate for protecting animal and human health. There is no suggestion that FDA's regulatory system is inefficient or that FDA does not have the expertise or legal authority to regulate GE animals. In fact, a recent U.S. District Court found that FDA was properly interpreting and applying its "animal drug" approval authority to GE animals.[8] FDA has invested significant resources to regulate GE animals and obtained the necessary staff with appropriate expertise. Before the federal government spends time and resources to create a new regulatory system for GE animals, it should explain how USDA oversight will be as protective as FDA's oversight as well as more efficient or effective. There should be a government analysis supporting the change and detailed discussions with interested stakeholders about the implications of that change. At present, USDA has failed to identify a problem, much less put forth a regulatory regimen that could fix it.

There may be benefits to USDA replacing FDA oversight of GE animals. For example, FDA's current system falls short in that: (1) it is not transparent; (2) it does not allow for public participation; and (3) it does not provide adequate authority to address environmental impacts (which for some GE animals could be significant). The federal government must establish that the new proposed system will maintain the current system's strengths while improving in the areas of transparency, public participation, and environmental protection. The undersigned groups support a federal mandatory pre-market approval process for GE animals that is transparent, participatory, and ensures human, animal, and environmental health and safety through risk assessment using scientific evidence, which could be at established at either FDA or USDA. There is insufficient information in the ANPR to determine if the proposed USDA regulatory system will meet those criteria and whether it will improve upon the FDA regulatory system and its shortfalls.

II. There is Insufficient Detail in the ANPR to Determine If GE Food Animals Can Be Adequately Regulated under the APHA

The ANPR proposes that USDA will regulate all potential non-food safety impacts of GE food animals (e.g., potential pest and disease risks) using the AHPA. However, there is insufficient detail in the ANPR to determine if APHA provides adequate authority for these purposes. The ANPR states that it would establish "end to end regulatory oversight from pre-

[8] See Institute for Fisheries Resources, et.al., v. Stephen Hahn, et.al. Case 3: 16-cv-01574-VC, District Court ND CA, 12/19/2019. The District Court decision upholds FDA's interpretation of its legal authority to regulate GE animals as "new animal drugs." That judicial decision will make it difficult for FDA to stop that oversight and defer to the regulatory framework proposed in the ANPR. If FDA does not approve a genomic alteration as a new animal drug, it could be sued for not carrying out the statute and developers could be found in violation of the FFDCA.

market reviews through post-market food safety monitoring" in "most instances." However, it does not explain in which instances it will not provide such review and what scientific evidence USDA will use to support a less thorough review for some GE food animals. While we support a tiered or proportionate review of GE food animals based on their potential risks, the ANPR does not discuss any criteria or scientific evidence that it will use to determine which products will not get "end to end regulatory oversight."

Additionally, the ANPR says that "the regulatory framework that USDA is considering would be conceptually similar to the recently updated USDA [SECURE] regulations…" The regulatory framework USDA utilized to regulate GE plants between the early 1990s and approximately 2012 regulated most, if not all, GE plants released into the environment. The new APHIS regulatory framework established by the SECURE rule, which was promulgated in May 2020, eliminates most GE plants from significant regulatory oversight. It establishes four categories of products which are exempt from oversight and allows developers to self-determine that they are exempt without any notice to USDA. In promulgating the SECURE rule, USDA provided little or no scientific evidence that the products covered by the exemptions pose no plant pest risks.

The ANPR states that USDA does not plan to implement the exemptions for GE food animals that they established for GE plants in the SECURE rule. It states that USDA "envision[s] that all amenable species modified or developed using genetic engineering and intended for agricultural purposes would be subject to permitting requirements … until they have undergone an expedited safety review or an animal health risk assessment…" However, the ANPR also specifically seeks comment on this issue, leaving open the possibility that USDA could propose a rule that provides exemptions like those in the SECURE rule. We agree with USDA that "current experience, biology, and breeding practices" justify a different regulatory system for GE food animals than GE plants and do not support establishing any broad exemption categories. However, if USDA does propose to provide proportionate and tiered review of different classes of GE food animals, the different procedures and assessments should be justified with scientific evidence of reduced levels of risk, not just by stating that the GE animals' potential risks are comparable to conventionally bred animals that have historically not been regulated (as was the approach in the SECURE rule).

Thirdly, the ANPR states that the proposed rules will provide permits for "controlled field trials to evaluate the animals." However, it also states that it will propose a two-tiered review system in which certain modifications "that are already known to occur in the gene pool of the species" will have an expedited safety review. How many different categories of GE food animals will qualify for the expedited safety review? Will GE food animals that complete the expedited review process need to obtain a permit for field trials? USDA's regulatory framework for GE plants provides an expedited safety review for many GE plants and does not require permits for most field trials of products that satisfactorily complete the expedited review. If USDA establishes a similar regulatory framework for GE food animals, oversight of many of those animals may be minimal and possibly not proportionate to a product's potential risks. If USDA does not regulate field trials, those trials could lead to animals that have not yet been

determined safe to eat entering the food supply or could cause our meat and poultry exports to be rejected by importing countries where those meat and poultry products are considered experimental and have not yet been approved. For these reasons, there is not enough detail about how USDA would regulate GE food animals under the APHA to determine if the proposed oversight would be adequate and protective.

III. The Legal Authority under the APHA May Not Adequately Cover All the Potential Risks to Animal Health Posed by GE Animals

As mentioned *supra,* the ANPR proposes the animal health risk assessments of GE animals would be conducted under the AHPA. Notably, the AHPA gives broad authority to the USDA to take actions to control "pests or diseases" of livestock, and the ANPR asserts that this includes "non-infectious diseases." However, unless USDA determines that it will interpret "non-infectious diseases" to include all potential health impacts to individual animals or herds as part of their assessment, they will miss assessing important potential impacts to GE food animals that currently are covered by FDA.

We support a broad definition of non-infectious diseases, to include negative physiologic health risks to individual animals or populations, which may not be adequately covered under the AHPA authority. For example, "double muscled" (which have a larger amount of muscle mass) GE swine made from editing a single gene may have leaner meat and improved meat yield per animal but may have increased health risks compared with conventional swine, such as birthing difficulty.[9] Other physiologic health risks may not be as apparent. Cattle have been genetically engineered to lack the prion protein to protect them from prion diseases such as bovine spongiform encephalopathy ("Mad Cow") and consumers from the human version, variant Creutzfeldt-Jakob disease.[10] These animals may not be viewed as carrying more disease risks than the existing cattle population under the current health assessment proposal. However, the full physiologic function of the prion protein is not known, and thus the potential ancillary health issues stemming from its removal are unknown. This is especially important considering how modern breeding and genetic technologies can quickly spread genetic traits through animal populations. Before GE animals are brought to market, potential physiologic health risks need to be fully evaluated and clearly identified to livestock producers who will integrate these animals and genetics into their herds. The ANPR does not give one confidence that USDA will read its authority broadly to cover the full range of potential risks from individual genetic changes.

In a similar vein, the ANPR proposes an expedited safety review for GE food animals with modifications that are "equivalent to what can be accomplished through conventional breeding practices," except in cases where animal health is known to be negatively affected or where there is a health claim attached. A narrow, pest- and disease-focused definition of health

[9] Cyranoski D. Super-Muscly Pigs Created by Small Genetic Tweak. *Nature News* (online). June 30, 2017. Accessed February 17, 2021. https://www.nature.com/news/super-muscly-pigs-created-by-small-genetic-tweak-1.17874

[10] Richt JA, Kasinathan P, Hamir AN, et al. Production of Cattle Lacking Prion Protein. *Nat Biotechnology*. 2007;25(1):132-138. doi:10.1038/nbt1271

for this expedited safety review could allow genetic alterations with serious physiologic health consequences to animals to enter the marketplace with ease. For example, similar to the cattle that were genetically engineered to have lost their prion proteins, a small population of goats was found to have a naturally occurring mutation to the prion gene which achieved the same effect. This occurred through traditional breeding practices. Under the ANPR's proposed expedited safety review process, prion-less genetics could quickly penetrate animal populations, with the associated potential animal health risks. Other modifications that could be theoretically achieved through traditional breeding practices, especially ones that have not previously been prevalent in animal populations, could likewise pose unknown physiologic health risks to animals. Therefore, all GE animals should undergo health risk assessments of all potential health impacts before commercialization, not solely potential pest and disease impacts.

IV. More Details are Needed to Determine if USDA Can Ensure the Food Safety of GE Food Animals Through Pre-Slaughter Food Safety Assessments

The ANPR proposes that USDA has the authority to ensure GE food animals are safe, wholesome, and not adulterated under the FMIA and the PPIA through a pre-slaughter food safety assessment. USDA admits that its inspectors would not be able to determine safety of these animals using currently available testing methodologies and inspection techniques used at slaughter and processing facilities.[11] Instead, USDA proposes that the developer would submit scientific data at some point before the animals enter the slaughter or processing facility for a food safety assessment. The proposal does not specify whether the review will occur before the animals are grown commercially (as is done currently by FDA) or while the animals are already growing on commercial farms but before they are slaughtered. In addition, there is no discussion in the ANPR about whether the scientific data submitted by the developer and USDA's food safety assessment will be released to the public for comment before USDA determines the meat or poultry can enter the food supply. If USDA moves forward to regulate GE food animals, the undersigned groups will only support USDA's regulatory framework if the agency conducts a thorough assessment of all potential food safety risks that is transparent, participatory, and completed prior to commercial release of the animals to farmers and ranchers.

[11] The ANPR states: "For animals of the amenable species modified or developed using genetic engineering, however, a FSIS inspector would likely be unable to make an 'on the spot' determination about whether the live animal should be segregated, or whether the meat or poultry product is adulterated at the time the animal is presented for inspection at the slaughter facility using currently available testing methodologies and inspection techniques. Live animals of the amenable species modified or developed using genetic engineering and their carcasses typically will not be distinguishable from conventionally produced animals based on their physical appearance. Also, there currently is no generally applicable test that could be administered in the slaughter facility to determine whether the animal was modified or developed using genetic engineering or whether the genetic modification would render the resulting meat or poultry product adulterated within the meaning of the statutes." (85 FR at 8427)

V. The Federal Government Needs to Ensure that GE Animals Are Not Regulated More Stringently or Leniently Solely Because They Are Regulated at One Agency Instead of Another.

Under the ANPR, USDA would regulate some, but not all, GE animals. For example, USDA would regulate cattle, pigs, poultry, and catfish while FDA would regulate all fish except catfish, seafood, and dairy products derived from cattle. FDA or USDA using different statutes, safety standards, and procedures could make the regulatory pathway for GE animals with comparable risk profiles significantly easier than others. For example, as stated earlier, if the AHPA regulatory oversight process only looks at potential pest and disease risks, it will be significantly narrower in its oversight than FDA's review of all potential animal health impacts. Similarly, based on statements in the ANPR, if a GE catfish and a GE salmon were created using gene editing, USDA might only require an expedited risk assessment for animal health for the GE catfish while the GE salmon under FDA jurisdiction would go through mandatory pre-market approval. In both examples, the differences in regulatory scrutiny and oversight would not be because one of the fish is less risky than the other, but solely due to the scope of the different laws, regulations, and how the agencies are implementing them.

Genetic engineering has the potential to introduce traits in food animal species with benefits to food chain actors ranging from farmers and ranchers to consumers. However, if one agency regulates GE food animals under its jurisdiction more stringently without an adequate scientific justification, developers might avoid species regulated by one agency or the other and only modify species that receive more lenient oversight. If the federal government wants to prioritize the development of certain GE animals, it should be done based on social need and benefits, not leniency of oversight. If USDA is going to regulate certain GE food animals, its oversight should be comparable to that of FDA unless there are specific species and/or traits warranting different levels of oversight supported by scientific evidence.

VI. The ANPR Would Establish Duplicative and Overlapping Regulatory Processes for Certain GE Animals that Would Require Submitting Applications to Both Agencies.

In December 2020, FDA approved a genetic alternation in a pig (GalSafe), where the developer had eliminated the alpha-gal sugar on the surface of the pig's cells (which for some people can be an allergen). FDA approved the Galsafe pig for use as both food and as a human therapeutic in their "new animal drug" regulatory approval process. The ANPR states that USDA would regulate agricultural purposes of food animals and FDA would regulate medical and pharmaceutical purposes of those same animals, meaning the GalSafe pig would be required to go through both USDA's regulatory system for the food application and FDA's new animal drug approval process for its human therapeutic application. This would be inefficient and could result in contradictory regulatory decisions if one agency approves the GE pig and the other does not. Similarly, the two agencies could impose different risk management obligations. Separating the jurisdiction of this animal (and other future animals like it) between two agencies will result in a more complicated regulatory system with no clear benefits beyond the current one.

As a second example, the ANPR states that USDA would regulate GE cows and the meat derived from them while FDA would regulate dairy products made from those animals. It is inconceivable that FDA could assess the food safety of dairy made from some GE animals (especially if the engineered trait impacts the cow's milk) without doing a thorough assessment of the whole GE animal and the introduced genetic changes. Again, the proposed oversight at USDA and FDA would be duplicative and potentially contradictory.

VII. All Unintended Changes in the DNA of a GE Animal Need to Be Investigated, Not Just Those in GE Animals Undergoing an Expedited Review.

The ANPR states that, in the expedited safety review, USDA will verify "that there were no unintended disruptions of endogenous genes, unintended DNA insertions, or off-target changes if the DNA was modified without inserting DNA." No comparable statement is made for the GE animals subject to the more thorough animal health risk assessment. The ANPR discusses an evaluation of the "molecular characterization" of the animal but there is no mention of any analysis of unintended disruptions/insertions or off-targets. When FDA conducted a genomic and phenotypic analysis of a genome-edited hornless bull, they found an unintended DNA insert of the template plasmid of which the developer was unaware.[12] FDA concluded from this discovery and its experience regulating GE animals that "genome editing in animals can have unintended consequences and that regulators must be alert to the possibility of such consequences."[13] FDA stated that:

> [T]here is good reason for regulators to analyze data on intentional genomic alterations in animals to determine whether there are any unintended results, either on- or off-target and, if so, to determine whether they present any cause for regulatory concern.[14]

Therefore, if USDA is going to regulate GE food animals, they must analyze and consider both unintended introductions of DNA and off-targets when they analyze the safety of each animal.

VIII. The Federal Government Regulatory System for GE Animals Needs to Assess and Manage Potential Environmental Risks.

The release of GE animals has the potential to adversely impact the environment. For example, GE pigs grown on U.S. farms might inadvertently interbreed with feral pig populations. If the GE pigs had a trait that increases fecundity or longevity, that trait in the feral pig population might exacerbate control of feral pigs, which already impose substantial environmental impacts and costs. Similarly, if a GE salmon were to escape from containment into U.S. waterways, it could have substantial impacts on native species or other fish species. The federal regulatory system for GE animals needs to assess potential environmental impacts

[12] Norris, A, et. al., "Template Plasmid Integration in Germline Genome-Edited Cattle," Nature Biotechnology, 38: 163-4 (February 2020).
[13] Solomon, S. "Genome Editing in Animals: Why Regulation Matters," Nature Biotechnology, 38:142-3 (February 2020).
[14] Solomon, S. "Genome Editing in Animals: Why Regulation Matters," Nature Biotechnology, 38:142-3 (February 2020).

and put in place risk management plans for risks that are identified. If a risk cannot be adequately managed, that GE animal should not be approved for commercial use.

FDA's current regulatory oversight using its "new animal drug" authority does not provide FDA with the ability to deny an approval based on unmanageable environmental risks. Instead, the FDA approval process must comply with the National Environmental Policy Act (NEPA) by assessing the impacts of each GE animal. However, NEPA provides no legal authority for FDA to require any actions to address the identified risks. The ANPR states that GE animals that require an animal health risk assessment under the AHPA will be reviewed to determine if compliance with NEPA is required. For GE animals that are granted the expedited safety review, the ANPR makes no mention of any assessment of potential environmental impacts. Neither FDA's current regulatory framework nor USDA's proposed framework assure adequate oversight of potential environmental impacts, but FDA at least assesses environmental risks for all applications. The ANPR proposes a review of environmental factors only for a subset of the GE animals it regulates under the AHPA (which is already a subset of GE animals that FDA would regulate – see section III above).

IX. **The MOU Between FDA and USDA is Inadequate and Should be Revised.**

If USDA regulates GE food animals, there is a need for a new memorandum of understanding (MOU) between FDA and USDA. First, FDA has significant expertise determining the human and animal health safety of GE animals and should have the opportunity to review the draft assessments performed by APHIS and FSIS and provide comments before they are finalized. Second, there is a need to ensure consistency of regulatory oversight for all GE animals. If both agencies are to review a product, FDA and USDA need to ensure that their reviews will result in consistent decisions. Thus, the MOU should be significantly revised if USDA proceeds with the rulemakings proposed in the ANPR.

We appreciate the opportunity to provide these comments to the USDA and would welcome the opportunity to meet with the staff at USDA to discuss the issues addressed here in more detail.

Sincerely,

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