Innovative Genomics Institute

August 5, 2019

Regulatory Analysis and
Development, PPD, APHIS,
Station 3A-03.8
4700 River Road Unit 118
Riverdale, MD 20737-1238

Re: **Docket No. APHIS-2018-0034: Movement of Certain Genetically Engineered Organisms**

Dear Sir or Madam,

The Innovative Genomics Institute (IGI) is pleased to submit these comments in response to the issuance of Proposed Rule 7 CFR Parts 340 and 372 "Movement of Certain Genetically Engineered Organisms" by the Animal and Plant Health Inspection Service (APHIS) (hereinafter, the "proposed rule"). We are grateful to the APHIS for their efforts to modernize the regulation of genetically engineered organisms, and appreciate the opportunity to contribute our expertise.

The Innovative Genomics Institute (IGI) is a non-profit, academic research organization formed through a partnership between the University of California, Berkeley and the University of California, San Francisco, two of the world's leading scientific research institutions. After co-inventing CRISPR-based systems for rewriting DNA, Jennifer Doudna founded the IGI to bring together researchers in diverse disciplines with a powerful combined expertise in order to apply this technology to address some of humanity's greatest challenges. We support academic research in Agriculture, Biomedicine, Microbiology, Technology development, and Society.

Our faculty, researchers, and staff have extensive experience in the discovery, development, and deployment of plant genome engineering technologies, and are leaders in genome editing in agriculturally relevant plants. In line with this expertise, we submit our comments with a focus on plants and genome editing.

We appreciate your consideration of our comments and are happy to discuss further if desired.

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IGI's Comments on Docket No. APHIS-2018-0034: Movement of Certain Genetically Engineered Organisms

Plant breeding innovations hold immense promise for food security, meeting the demands of climate change and growing populations, as well as addressing farmer and consumer desires of their food systems. In the past decades, the large regulatory burden placed on plants produced using genetic engineering has limited both the variety of traits being developed, as well as the developers in the marketplace. At the same time, 30 years of evidence and advances in techniques have made it clear that some aspects of that burden are no longer scientifically justified.

We appreciate the agency's effort to modernize its regulations of genetically engineered organisms. As APHIS points out, if finalized, this proposed rule would represent the first major re-working of the regulations since they were created over 30 years ago. Such an update is much needed, particularly in light of new plant breeding technologies such as genome editing, which unlike their predecessors, don't necessarily use plant pest sequences to enact changes to a plant genome. In light of the scope of the proposed rule, we echo the many requests that the **comment period be extended an additional 60 days** to allow adequate time for stakeholders to thoroughly consider the agency's proposal. In addition to this request, we offer the following comments.

Removal of plant-pest-derived DNA regulatory trigger

The use of a sequence derived from a plant pest or pathogen has been the regulatory trigger for the USDA for the past 30 years; a logic that was born out of limited knowledge at the time of the recombinant DNA revolution and discovery of agrobacterium as a delivery vector for plant engineering. In the years since, our understanding of DNA and genomics, as well as real-world evidence gained through use of recombinant DNA for over a quarter of a century by academia and industry has made it clear that, as APHIS asserts, the source of the DNA sequence does not itself pose a risk to plants, but rather the conferred attribute/trait and mechanism of action convey the risk[1]. We thus support the removal of this regulatory trigger and the recognition that there is now a history of safe use of agrobacterium and common pathogen-derived regulatory sequences to where their use should not automatically require that a plant be regulated by APHIS under 7 CFR part 340.

Product over process

The Coordinated Framework for Regulation of Biotechnology asserts that products intended for release in the environment should be regulated based on the characteristics of the product and its intended use, not the process by which it was made[2]. While the proposed rule still relies on the process of genetic engineering as a trigger for regulatory consideration, the proposed changes to 7 CFR part 340 better reflect the Coordinated Framework's policy, and are upheld by the science as stated above.

Exemptions in § 340.1(b)

With these exemptions, APHIS attempts to codify, in practical terms, Secretary Perdue's statement on new breeding technologies that could otherwise be produced using conventional breeding methods. The logic here is sound. If products of conventional breeding are not regulated (and will not be regulated), then it stands that if a product is created using genetic engineering that could be created using conventional breeding, then it should not be regulated differently. The details, however, of how to systematically exempt those products from part 340 are not obvious. We suggest the following consideration:

> What kinds of changes can be made with conventional breeding? These methods rely on natural variation in the gene pool, the rate of mutation in populations, and induced mutation using chemical or physical mutagens. Mutations produced through conventional breeding are not just deletions or single base pair substitutions, they include the result of spontaneous or induced double-strand breaks (DSB). These breaks often result in a distribution of indels following non-homologous end joining (NHEJ)[3]. Similarly, new breeding techniques such as genome editing rely on natural repair pathways often resulting in indels after inducing DSBs[4]. Thus, it is not clear that single base-pair substitutions or deletions of any size would be exempted whereas other products of NHEJ would not. We understand that it is difficult to define a reportable sequence characteristic that could be used to systematically determine if a modification is the result of NHEJ and therefore capable of being produced using

conventional breeding methods. However, we recommend that the agency consider exempting a sequence characteristic beyond a deletion or single base pair substitution.

Abandoning event-by-event evaluation
The requirement to approach APHIS for evaluation every time the same genetic modification is made in the same plant stems from earlier concerns that each new integration event could have a different impact on the plant which could pose new safety concerns. As APHIS asserts, 30 years of data on these events have not born this concern out. What's more, new breeding techniques such as genome editing rely on targeted changes to the genome which, by virtue of their mechanism of action, create changes at a defined and reproducible location, making the rationale for requiring new regulatory evaluation upon every new transformation event irrelevant. We thus support the removal of this event-by-event evaluation in the proposed rule as it only serves to increase regulatory burden with no added safety benefit.

Self-determination step
The success of a new innovation is linked in part to trust at many levels of the process[5,6]. Trust in the regulations and regulators to adequately ensure safety is just as important as trust in the developers of the products[a]. While we recognize the agency's rationale behind self-determination and desire to provide regulatory relief in order to spur innovation, we are concerned that rather than stimulating innovation, such an undisclosed step may have the effect of dampening trust through the loss of transparency in the development and oversight process. We suggest that rather than an un-reported self-determination step, the agency consider amending their proposed rule to include a streamlined self-reporting process that feeds into the proposed database of products that have gone through regulatory status review. Having a complete database of all products, regardless of further regulatory status, will build public confidence in the regulatory system and have the added benefit of assisting in the enforcement of regulations (discussed below), as well as providing a resource for the scientific community[7].

Enforceability
One of the assets of new breeding technologies like genome editing is the ability to scarlessly create genetic changes that are indistinguishable from what could theoretically be achieved using traditional breeding - but in a fraction of the time and with less risk of unintended genetic alterations. This indistinguishability simultaneously makes the scientific case that products of these breeding technologies are not inherently different than their conventionally bred counterparts, but it also makes detection and enforcement of rules pertaining to products of genetic engineering exceedingly difficult. In § 340.6(c), it is not clear how the proposed rule will be enforced in those cases where the modified plant is regulated but not obviously unachievable by traditional breeding.

Of particular concern is the plan for detection and enforcement for those that incorrectly self-determine to be un-regulated, or where changes in evidence may call a self-determination into question. Without a record of what plants are being released, it will be impossible to conduct any kind of periodic surveillance or audit to ensure compliance. This difficulty may be partly addressed by having a compulsory reporting mechanism described above whereby a responsible party fills out a form to declare their modification and assert its exempt status. A self-reporting database would not fully protect against bad actors but would aid in correcting miss-assessments during self-determination.

Presumably, the inclusion of the threat of stiff penalties for incorrect self-determination is proposed to help ensure compliance in the absence of reporting, however, it may also have the effect of discouraging self-determination, and lead to an abundance of requests for confirmation of self-determination. This would undo the administrative relief provided by the inclusion of this step. Addition of a mandatory self-reporting step to create a searchable record, combined with penalties that are proportional to the degree of harm done by incorrectly self-determining may help resolve this issue.

[a] Secretary Perdue has touted the importance of public confidence, stating, "It's critical that our regulatory requirement foster public confidence and empower American agriculture while also providing industry with an efficient and transparent review process that doesn't restrict innovation…". Press Release No. 0144.17

Specific Line Comment
§ 340.4 (a)(4) Lists the information that must be submitted "in support of a request for a regulatory status review or re-review". Under (ii), the agency states, "The genotype of the modified plant, including a detailed description of the differences in genotype between the modified and unmodified plant;"

- What level of sequencing is needed here? Does the agency wish to have whole genome sequencing, information on off-targets, or only sequencing of the target of the modification? As written, it is not clear what type of data the agency expects.

We appreciate the opportunity to provide feedback on the proposed rule, and would welcome any inquiries by the agency to further discuss these comments.

[1] National Academies of Sciences, Engineering, and Medicine. 2016. *Genetically Engineered Crops: Experiences and Prospects*. Washington, DC: The National Academies Press. doi: 10.17226/23395.

[2] 2 1992 Update to the Coordinated Framework, 57 FR at 6753.

[3] Manova, Vasilissa and Damian Gruszka. 2015. "DNA Damage and Repair in Plants – From Models to Crops." *Frontiers in Plant Science* 6(e88872):187.

[4] Carroll, Dana. 2014. "Genome Engineering with Targetable Nucleases." *Annual Review of Biochemistry* 83(1):409–39.

[5] Dovey, Ken. 2009. "The role of trust in innovation", *The Learning Organization,* Vol. 16 No. 4, pp. 311-325. https://doi.org/10.1108/09696470910960400

[6] Siegrist, Michael, Marie-Eve Cousin, Hans Kastenholz, and Arnim Wiek. 2007. "Public Acceptance of Nanotechnology Foods and Food Packaging: the Influence of Affect and Trust." *Appetite* 49(2):459–66.

[7] Chapter 9 "Regulation of Current and Future Genetically Engineered Crops." National Academies of Sciences, Engineering, and Medicine. 2016. *Genetically Engineered Crops: Experiences and Prospects*. Washington, DC: The National Academies Press. doi: 10.17226/23395.