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COMMENTS OF ITIF

to the

Animal and Plant Health Inspection Service
US Department of Agriculture

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Attn: Alan Pearson

In response to:	)	
The White House Office of Science and Technology Policy (OSTP)	)	
Request for Information on:	)	Docket ID No. APHIS-2022-0076
Identifying Ambiguities, Gaps, Inefficiencies, and Uncertainties in the Coordinated Framework for the Regulation of Biotechnology	)	

January 27, 2023

INTRODUCTION

Over the past decade, successive administrations have several times solicited public comments on the same subject matter covered in the present request for information (RFI). And while biotechnologies have seen remarkable, rapid advances and the discovery and development of powerful new techniques (i.e., CRISPR-mediated gene editing; gene drives), nothing has changed fundamentally in any way that presents new or unique hazards, and the same steps long required to streamline and improve relevant regulations remain valid, albeit even more urgent than before. We and many others have responded to these solicitations with recommendations rooted in the principles foundational to the Coordinated Framework.[1] While the comments and recommendations in these submissions remain valid and timely, we nevertheless provide here fresh comments in response to the latest RFI.

COMMENTS AND RECOMMENDATIONS

The questions posed by OSTP are presented in italics, with the answers below.

1. *Describe any ambiguities, gaps, inefficiencies, or uncertainties regarding statutory authorities and/or agency roles, responsibilities, or processes for different biotechnology product types, particularly for product types within the responsibility of multiple agencies.*

The most important imperfections in the U.S regulatory system for biotechnology products do not stem from "gaps, inefficiencies, or uncertainties regarding statutory authorities and/or agency roles, responsibilities, or processes for different biotechnology product types, particularly for product types within the responsibility of multiple agencies," but rather from faulty application in regulations and guidance documents of the principles laid out in the Coordinated Framework. Since 1992, none of the regulatory agencies have streamlined or updated their regulatory procedures to a degree commensurate with the lessons learned in the interval, in accord with accrued experience and data. All have drifted away from approaches based on bedrock principals of sound regulation foundational and integral to the Coordinated Framework, specifically:

- The goal of regulation is not to achieve zero risk, but to avoid unreasonable risk.
- Risk results from exposure to a hazard.
- In the absence of an identified, credible hazard there is no valid risk hypothesis, and thus no risk to manage or mitigate. Regulation would thus have no potential for improving safety and would therefore be unjustified.

[1] ITIF Comments on USDA's Latest Proposal to Revise and Update Regulations for Crops Improved Through Biotechnology Including Gene Editing, August 5, 2009, https://itif.org/publications/2019/08/05/itif-comments-usdas-latest-proposal-revise-and-update-regulations-crops/; ITIF Comments to Food and Drug Administration on Gene-Edited Plants, June 14, 2017, https://itif.org/publications/2017/06/14/comments-food-and-drug-administration-gene-edited-plants/; ITIF Comments to U.S. Department of Agriculture's Animal and Plant Health Inspection Service on Genetically Engineered Organisms, June 14, 2017, https://itif.org/publications/2017/06/14/comments-us-department-agricultures-animal-and-plant-health-inspection/; ITIF Comments to FDA on Proposal to Regulate Gene-Edited Animals, April 17, 2017, https://itif.org/publications/2017/04/17/comments-fda-proposal-regulate-gene-edited-animals/.

- The degree of regulatory oversight, and measures for mitigation and management, must be proportional to the degree of risk, which is itself contingent on the quality and magnitude of the hazard.

A gene from one evolutionary lineage inserted into a genome from another does not itself constitute a hazard – we find myriad harmless examples of such wherever we look for them in nature. Commingled genomes are clearly mother nature's preferred configuration. Similarly, mutations that create changes in gene sequences that alter the sequence of amino acids in or expression of structural proteins are also not intrinsically hazardous; in each of these cases whether or not a hazard results depends entirely on the resulting phenotype, which is not predictably related to the underlying DNA sequence changes, which are hence not a legitimate or useful trigger for regulation.

Where a gene comes from has no bearing on whether the phenotype to which it contributes presents a hazard to which exposure can generate a possible risk. The characteristics of a gene are important only insofar as they contribute to a phenotype to which exposure would be hazardous, and not all exposures will create risks. Experience has shown, for example, that disease resistant and herbicide tolerant crops, nitrogen-fixing microbes, microalgae for biofuels, and improved farm animals are all highly impactful technologies that are zero or low risk. It has been obvious for years that these (and others) should be exempted from the present levels of oversight via categorical exemptions. But they are presently captured for review by EPA or FDA/CVM because of a procrustean application of regulatory authorities that ignores their amply demonstrated lack of hazards.

When the Coordinated Framework was promulgated in 1986, some of these facts were not well established. They are now indisputable. And with these observed facts of nature kept in mind, it is clear that none of the regulatory agencies are applying regulatory oversight to biotechnology products in a manner consistent with the principles listed above, though USDA comes closest. EPA has expanded its purview through tendentious interpretations of definitions that expand its mandate in ways Congress did not intend, which expand its regulatory mandate with little or no safety benefit.[2] Meanwhile, FDA/CVM, on the other hand, has strayed the farthest, as we have noted in detail, which comments we incorporate here by reference.[3]

a. Describe the impact, including economic impact, of these ambiguities, gaps, inefficiencies or uncertainties.

The impact of the failings described is that biotechnology mediated agricultural innovations are subject to disproportionate regulatory burdens that do little or nothing to improve human or environmental safety. They do, however, discourage, delay, and deter the development and introduction of solutions derived from the use of the most cutting edge and safest genetic improvement technologies in history to some of the most urgent problems presently facing humanity. Perpetuated reliance on older, less safe and sustainable products is

[2] John J. Cohrssen, "Regulating the Regulator of Plant Growth Regulators," *Regulation* (Cato Institute, Winter 2022–23), https://www.cato.org/regulation/winter-2022-2023/regulating-regulator-plant-growth-regulators.

[3] ITIF Comments to FDA on Proposal to Regulate Gene-Edited Animals, April 17, 2017, https://itif.org/publications/2017/04/17/comments-fda-proposal-regulate-gene-edited-animals/; ITIF Comments to Food and Drug Administration on Gene-Edited Plants, June 14, 2017, https://itif.org/publications/2017/06/14/comments-food-and-drug-administration-gene-edited-plants/.

thus unnaturally extended, to the detriment of human and environmental welfare. This is a policy that requires correction.

2. *Provide any relevant data or information, including case studies, that could inform improvement in the clarity or efficiency (including the predictability, transparency, and coordination) of the regulatory system and processes for biotechnology products.*

Relevant information, including case studies, that should inform improvement in the clarity and efficiency of the U.S. regulatory system has been plentiful for many years, from both the government itself and external.[4] Arguably one of the most succinct and concrete summaries of actions the administration should take has been captured in previous comments, which are incorporated here by reference.[5]

3. *Describe any specific topics the agencies should address in plain language on the regulatory roles, responsibilities, and processes of the agencies.*

The challenges that must be overcome to accomplish the stated aims of the RFI have little or nothing to do with "topics the agencies still need to address in plain language on the regulatory roles, responsibilities, and processes of the agencies" and everything to do with the ongoing failure of agencies substantively to correct their drift away from the principles of the Coordinated Framework as we have described. The present challenge is not one of public relations and communication but of substantive policy repair.

4. *Describe any specific issues the agencies should consider in developing a plan to implement regulatory reform, including any updated or new regulations or guidance documents.*

See Answers 2 and 3 above.

The administration will, no doubt, receive numerous comments from vested interests who reliably oppose any applications of innovative biotechnologies to the improvement of seeds, livestock, or other areas in which humans harness biological processes. The usual suspects will claim in their comments that recombinant DNA technologies, in particular gene editing, are too powerful and inherently dangerous to be unleashed on

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[4] See, e.g., National Academies of Sciences, Engineering, and Medicine; Division on Earth and Life Studies; Board on Chemical Sciences and Technology; Board on Agriculture and Natural Resources; Board on Life Sciences; Committee on Future Biotechnology Products and Opportunities to Enhance Capabilities of the Biotechnology Regulatory System. Preparing for Future Products of Biotechnology. Washington (DC): National Academies Press (US); 2017 Jun 28. 3, The Current Biotechnology Regulatory System. Available from: https://www.ncbi.nlm.nih.gov/books/NBK442204/; Hygeia Analytics, "CEQ and OSTP Assessment: Case Studies of Environmental Regulations for Biotechnology," 2016, https://hygeia-analytics.com/wp-content/uploads/2016/12/RP_RegGETech_CEQ.pdf; "National Strategy for Modernizing the Regulatory System for Biotechnology Products," a product of the Emerging Technologies Interagency Policy Coordination Committee's Biotechnology Working Group (National Science and Technology Council, September 2016), https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/biotech_national_strategy_final.pdf.

[5] Val Giddings, "How the Biden Administration Can Accelerate Prosperity by Fixing Agricultural-Biotech Regulations" (ITIF, March 2021), https://itif.org/publications/2021/03/31/how-biden-administration-can-accelerate-prosperity-fixing-agricultural/; ITIF Comments on USDA's Latest Proposal to Revise and Update Regulations for Crops Improved Through Biotechnology Including Gene Editing, August 5, 2009, https://itif.org/publications/2019/08/05/itif-comments-usdas-latest-proposal-revise-and-update-regulations-crops/.

humanity despite the fact that decades of such claims have been contradicted by massive data and vast experience. Such demands for unduly burdensome precautionary regulation should be set aside as a policy that has been repeatedly tested and failed, as is widely recognized in myriad appraisals, a few of which we cite here and which are incorporated by reference.[6]

In considering public comments on proposals to streamline regulations for biotechnology products, OSTP and agencies should adhere to the principles of sound regulation as laid out in the Coordinated Framework in 1986 and Answer 1 above, and hold fast to the recognition that until and unless hazards are identified that are novel and unique to the products of recombinant DNA and gene editing, regulatory approaches that single them out for scrutiny above and beyond that applied to the fruits of older methods of genetic improvement cannot be justified on the basis of science or any concern for human welfare. Such approaches should be set aside.

Agencies should instead reconsider their approach to identifying triggers for regulatory oversight that hinge upon the presence of actual (as opposed to hypothetical or imaginary) hazards that translate into actual risks, remembering that risks can be managed or mitigated as appropriate, as we have described in detail and which we incorporate by reference.[7]

5. *Describe any new or emerging biotechnology products (e.g., microbial amendments to promote plant growth; food plants expressing non-food substances or allergens from non-plant sources) that, based on lessons learned from past experiences or other information, the agencies should pay particular attention to in*

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[6] U.K. Department for Business, Energy & Industrial Strategy, "Regulatory Horizons Council report on genetic technologies," September 1, 2021, https://www.gov.uk/government/publications/regulatory-horizons-council-report-on-genetic-technologies; European Commission, Directorate-General for Research and Innovation, Group of Chief Scientific Advisors, A scientific perspective on the regulatory status of products derived from gene editing and the implications for the GMO Directive : statement by the Group of Chief Scientific Advisors, Publications Office, 2019, https://data.europa.eu/doi/10.2777/407732; Josep M. Casacuberta and Pere Puigdomènech, "Proportionate and scientifically sound risk assessment of gene-edited plants," *EMBO Reports* (2018)19:e46907 https://doi.org/10.15252/embr.201846907; Science Media Centre, "expert reaction to Court of Justice of the European Union ruling that GMO rules should cover plant genome editing techniques," July 25, 2018, https://www.sciencemediacentre.org/expert-reaction-to-court-of-justice-of-the-european-union-ruling-that-gmo-rules-should-cover-plant-genome-editing-techniques/; European Academies Science Advisory Council, "Planting the future: opportunities and challenges for using crop genetic improvement technologies for sustainable agriculture," June 27, 2013, https://easac.eu/publications/details/planting-the-future-opportunities-and-challenges-for-using-crop-genetic-improvement-technologies-for-sustainable-agriculture/; UK Advisory Committee on Releases to the Environment, "Report 1: Towards an evidence-based regulatory system for GMOs," https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/239839/an-evidence-based-regulatory-system-for-gmos.pdf; Helen Albert, "GMO Regulations in Europe Are 'Not Fit for Purpose'" (Labiotech, November 11, 2020), https://www.labiotech.eu/in-depth/gmo-regulations-europe/; Mark Lynas, "Scientific community defeated by green groups in European court ruling on gene edited crops" (Alliance for Science, July 26, 2018), https://allianceforscience.org/blog/2018/07/scientific-community-defeated-green-groups-european-court-ruling-gene-edited-crops/.

[7] ITIF Comments on USDA's Latest Proposal to Revise and Update Regulations for Crops Improved Through Biotechnology Including Gene Editing, August 5, 2019, https://itif.org/publications/2019/08/05/itif-comments-usdas-latest-proposal-revise-and-update-regulations-crops/.

their evaluation of ambiguities, gaps, or uncertainties regarding statutory authorities and/or agency roles or processes.

We have answered this question in detail in responding to previous requests for public comment.[8] Those comments remain highly relevant to the present RFI and we incorporate them here by reference. Distilled, they show that the only new or emerging products to which agencies should pay particular attention are those associated with novel hazards with a significant likelihood they may present unreasonable risks if not managed or mitigated. Any proposals to manage or mitigate such risk must be based on confirmation that the relevant hazard is real, not hypothetical or conjectural. Uncertainty in such situations with respect to novel hazards can justify a request for data or experience. It cannot justify draconian prior restraint on well-designed research and development activities that would deliver solutions to urgent problems and provide answers to salient questions. Furthermore, to be consistent with the Coordinated Framework, the burden is on regulatory agencies to define a class of hazards in need of management or mitigation to avoid unacceptable risk. The burden must not be placed (as FDA does in its proposals to regulate gene edited animals and plants) on the innovator to prove an innovation safe in the absence of any credible risk hypothesis.

An example will illustrate the latter problem. In its proposal for regulating gene edited animals, FDA would require the innovator to demonstrate that phenotypes achieved through gene editing that are indistinguishable from those found in nature, and widely recognized as posing no unreasonable risks, would be required to be proven safe before they could be introduced to commerce.[9]

This is upside down and clearly a betrayal of the letter and spirit of the policy laid out in the Coordinated Framework. Instead, to be in accord with the Coordinated Framework, FDA must identify classes of hazards unique to products of gene editing that would create unacceptable levels of risk on exposure which would then justify imposition of proportional measures to manage or mitigate. This FDA has not done.

6. *Describe any new or emerging categories of biotechnology products on the horizon that the regulatory system and processes for biotechnology products should be preparing to address. Describe any specific recommendations for regulating these new or emerging categories of biotechnology products to guide agency preparations.*

It is not clear that any of the new or emerging categories of biotechnology products present novel hazards the exposure to which would precipitate unacceptable risks requiring management or mitigation. The historical record with products of genetic engineering and gene editing suggests such novel hazards are unlikely to be identified, because they are rare or absent. One novel application of genetic manipulations with which regulatory agencies may lack a comfortable level of experience, however, involves gene drives. These harness genetic mechanisms identified in nature and long studied but which have only recently begun to be adapted

[8] ITIF Comments on USDA's Latest Proposal to Revise and Update Regulations for Crops Improved Through Biotechnology Including Gene Editing, August 5, 2019, https://itif.org/publications/2019/08/05/itif-comments-usdas-latest-proposal-revise-and-update-regulations-crops/.

[9] See Dr. Alison Van Eenennaam, "Regulation of Genetically Modified Animals" *Biobeef Blog,* December 28, 2020, https://biobeef.faculty.ucdavis.edu/2020/12/28/regulation-of-genetically-modified-animals-part-1/.

into potential products for use by humans.[10] Agencies must take care, however, to identify actual hazards likely to present unreasonable risks, and to devise proportional measures to manage or mitigate them. And once again, the goal is not to achieve zero risk, but avoid unreasonable risks. Outright prohibitions are not proportional measures.

7. *What is the highest priority issue for the agencies to address in the short term (i.e., within the next year) and in the long term?*

The highest priority issue for agencies to address in the near term is the fact that, without exception, agencies' existing approaches to regulating products of genetic engineering and gene editing are disproportionate. They impose a degree of regulatory oversight that is not linked to actual hazard, which is contradicted by experience, and which disincentivizes the development of urgently needed tools without delivering commensurate improvements to environmental safety or human welfare.

All regulatory agencies need to recalibrate their regulatory oversight of biotechnology products to narrow the chasm that has arisen between the regulatory burden imposed on biotechnology products and the actual risks they entail, which vast experience has shown, in the absence of novel or unique hazards, is in most cases effectively nil.

Sincerely,

/s/ L. Val Giddings, Ph.D.
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[10] See: Ronald Aylmer Fisher, *The genetical theory of natural selection* (Oxford: Clarendon Press, 1930), https://doi.org/10.5962/bhl.title.27468; Francisco Úbeda, Manus M. Patten, and Geoff Wild, "On the origin of sex chromosomes from meiotic drive," *Proceedings of the Royal Society B*, January 7, 2015, https://doi.org/10.1098/rspb.2014.1932; Terrence W.Lyttle, "Cheaters sometimes prosper: distortion of mendelian segregation by meiotic drive," *Trends in Genetics*, Volume 9, Issue 6, 1993, pages 205-210, ISSN 0168-9525, https://doi.org/10.1016/0168-9525(93)90120-7.