Innovative Genomics Institute

Re: APHIS-2022-0076

Request for Information: Identifying Ambiguities, Gaps, Inefficiencies, and Uncertainties in the Coordinated Framework for the Regulation of Biotechnology

February 3, 2023

Attn: Alan Pearson
Animal and Plant Health Inspection Service, US Department of Agriculture
4700 River Road, Riverdale, MD 20737
alan.pearson@usda.gov

Dear Sir or Madam,

The Innovative Genomics Institute is pleased to submit the below comments in response to the Request for Information on Identifying Ambiguities, Gaps, Inefficiencies, and Uncertainties in the Coordinated Framework for the Regulation of Biotechnology

The Innovative Genomics Institute (IGI) is a public, academic research organization formed through a partnership between the University of California, Berkeley and the University of California, San Francisco. After making the transformational breakthrough discovery of bacterial genome editing systems known as CRISPR that can be applied to human, plant, animal, and microbial cells, Dr. Jennifer Doudna founded the IGI with the goal of bringing together scientists and innovators from diverse disciplines to unlock the potential of CRISPR to solve some of humanity's greatest challenges.

We drive research in agriculture, biomedicine, microbiology, and biotechnology development. The IGI has a dedicated Public Impact team that focuses on matters of science policy, regulation, and societal engagement to ensure the responsible, ethical, and equitable deployment of CRISPR technologies.

We included varied academic perspectives from several IGI and IGI-affiliated researchers (see **Contributors**). We are grateful for the opportunity to provide input and recommendations to USDA, FDA, and EPA, as well as the Office of Science and Technology Policy to help mitigate uncertainties and enhance the academic community's understanding of applicable laws and regulations.

The IGI stands ready to further lend its expertise and answer any questions that may arise about the comments below.

On behalf of the Innovative Genomics Institute,

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There is tremendous potential to solve societal problems through biotechnological innovation and the Innovative Genomics Institute and its affiliated researchers are encouraged by the Biden Administration's leadership in this space. Rapid advances in cell and gene therapy have had outsized impacts on health, making cures for a broad range of genetic diseases an achievable reality. Agricultural crop plants can be genome edited with relative ease to increase yield, confer pest, drought, and flood resistance, and remove toxins from staple foods. An enhanced understanding of microbial life is revealing biological processes that can be leveraged to produce innovative solutions to climate change. Below we outline emerging research areas that (will) require clear regulatory guidance as well as ways to facilitate how regulatory developments are communicated to the academic community.

Ambiguities, gaps, inconsistencies, and uncertainties in the Coordinated Framework (Q.1)

Researchers working on new tools and biotechnologies have identified a number of ambiguities, uncertainties, and gaps in the Coordinated Framework:

- The greatest source of ambiguity and uncertainty among academic developers results from difficulty identifying which regulations and guidances pertaining to the Coordinated Framework are most current. Given the multi-agency oversight of biotechnologies under development, and frequent policy updates, it is essential for information to be temporally organized and accessible in a single location. It would be additionally helpful to highlight how a new guidance amends a previous one.

  As others have pointed out[1], further development of a user-friendly Unified Website for Biotechnology Regulation[2] is key to facilitating the regulatory process for developers. There is a unified website but it is not frequently updated. The Unified Website should be leveraged to provide updates to stakeholders, such as guidance documents, notices to RFIs, listening sessions, and so on. A joint listserv for which stakeholders can sign up to receive updates related to the Coordinated Framework would be very useful. Currently the onus is on developers to navigate a complex and fast-evolving multi-agency system. Given the fragmentation of the system, the establishment of a cross-cutting biotechnology council that evaluates emerging product categories and communicates updates could be an effective way to reduce inefficiencies, close gaps, and tackle ambiguities.

- In the long term, the US government should work towards a unified submission process through which FDA, EPA, and USDA coordinate product reviews and assign agency jurisdiction.

- For genomic therapies, it is critical that FDA provides guidance on how it will regulate gene-editing products that target the same gene, but with different guide RNA spacer sequences. This applies, for example, when treating individuals with different mutations in the same gene that lead to a

[1] https://www.schmidtfutures.com/wp-content/uploads/2022/04/Bioeconomy-Task-Force-Strategy-4.14.22.pdf
[2] https://usbiotechnologyregulation.mrp.usda.gov/biotechnologygov/home/

single, clinically-defined disease. Clarity in this area is key to platformizing CRISPR-based therapeutics.

- Guidance on how to effectively and safely advance N-of-1 and N-of-few therapeutics is urgently needed. With advances in sequencing identifying unique mutations and precision medicines moving at a rapid pace, it is an unsustainable investment of resources to seek regulatory authorization before dosing of every individual affected by an ultra-rare disease. We recognize the challenges that N-of-1 therapies pose and are encouraged that FDA is carefully evaluating how to best proceed to establish an adequate regulatory framework[3]. The IGI stands ready to lend its expertise to help advance this goal.

- The distributed and point-of-care manufacturing of cell and gene therapy products requires clear FDA guidance. These methods are already proving to lower cost and increase access to life-saving therapies and clear regulatory frameworks are needed for further implementation.

- It would be of great benefit for regulatory steps and timelines to be clear, and the approvals process timely. While we recognize that a robust and stringent review process is particularly important for products intended to be released into non-managed environments (e.g. pest-resistant varieties of native trees), it will be key to develop clear and timely processes as more products in this category are under development (also **Q.6**). Important lessons can be learned from the regulatory process for the genetically engineered American chestnut tree.

Impacts of uncertainties (Q.1a)

Uncertainties and ambiguities in the U.S. regulatory system have led to wasted time and resources, delays, and difficulty obtaining approval.

- Due to the expensive regulatory approval process and negative public perception of GMO products, academic researchers and smaller companies have lost significant time, effort, and resources in the development of GMO products that are not commodity crops. For example, IGI and IGI-affiliated researchers have developed faster germinating barley, hypoallergenic wheat, and more digestible sorghum varieties that lacked the necessary financial support to move through the approvals process. The hope with CRISPR genome editing is that these types of products can be brought to market without facing such challenges. It is therefore essential that information about regulations and guidances is clearly communicated to researchers in order for them to incorporate these considerations into product designs and avoid wasting time and resources (also **Q.3**).

[3] https://www.nejm.org/doi/full/10.1056/NEJMe1911295#.XZ5PBIEjDIY.twitter

Need for plain language explanations (Q.3)

Academic scientists are often unaware of the nuanced distinctions between gene-edited crops that are exempt from regulations and those that are not. Some are misinformed and believe CRISPR-mediated editing is exempt from regulatory oversight altogether. In addition, they are not used to legalese and face challenges keeping up with the fast-changing regulatory environment. It is essential for academic researchers to have clear guidance in plain language on the types of edits that can be made without triggering regulatory review to inform how they approach product development. As indicated above as a high priority (also **Q.7**) and method to reduce inefficiencies and gaps, the Unified Website could serve as a central hub for all plain language summaries as well as a way to effectively communicate critical developments, such as updated guidances with stakeholders.

It would further be particularly helpful if FDA, EPA, and USDA attached plain language summaries to their regulations, guidances, and other technical documents. For researchers that want to learn more about the path of a product to market, easily accessible and understandable tools to learn more about the process would be helpful.

Emerging categories of biotechnology products (Q.6)

We identified several emerging categories of products and tools for which regulatory frameworks will need to be clarified in the future.

- Genetically engineered microbes: As genome editing and engineering technologies in microbial communities *in situ* are under investigation for human and environmental applications, it will be critical to establish adequate regulatory frameworks to safeguard people and the planet while also enabling responsible innovation. These technologies could come in several forms, such as the delivery of genome engineering tools to a microbiome to edit one or more bacterial species (e.g., the human gut microbiome, the cow rumen, manure lagoons, etc.) or as the introduction of one or more genetically engineering microbes into a microbiome. Regulatory frameworks are needed for different contexts and use cases and clarity is needed to understand what types of edits are considered genetic engineering vs present naturally or in the microbial gene pool. Efficient risk/safety assessments are also needed, for example using metagenomic sequencing. On this front, we are encouraged by and grateful for the participation of USDA, FDA, and EPA in the February 2022 virtual workshop on this topic.
- N-of-1 and N-of-few cell and gene therapies (see above)
- Distributed and point-of-care manufacturing for cell and gene therapies (see above)
- Biotechnological alternatives to antimicrobials in animals
- Biotechnological products to improve feed efficiency in livestock
- Engineered organisms released into non-agricultural, natural, or unmanaged environments

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Conclusion

The Innovative Genomics Institute is grateful for the opportunity to provide input to the FDA, EPA, and USDA on how to reduce uncertainties and ambiguities in the Coordinated Framework. As developers of biotechnologies for applications in humans, animals, plants, and the environment, we are committed to deploying these tools in a socially responsible manner. We identified several key gaps and uncertainties that our researchers face as well as emerging biotechnologies for which clear regulatory frameworks will be needed. Plain language explanations of regulations and timely updates of new guidances would be particularly helpful to academic scientists to inform product development.

We are encouraged by this Request for Information and look forward to seeing updates to the Coordinated Framework.

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