EBRC Engineering Biology Research Consortium

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

An EBRC Response to OSTP RFI; 87FR77900

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The Engineering Biology Research Consortium (EBRC) is pleased to submit this response to the Office of Science and Technology Policy's Request for Information (RFI) on *Identifying Ambiguities, Gaps, Inefficiencies, and Uncertainties in the Coordinated Framework for the Regulation of Biotechnology*. EBRC is a non-profit, public-private partnership dedicated to bringing together an inclusive community committed to advancing engineering biology to address national and global needs. EBRC members represent diverse perspectives of the engineering biology research community and include some of the nation's top scientists and engineers. EBRC is thrilled to see the development of the National Biotechnology and Biomanufacturing Initiative and the attention being given to regulatory considerations. We are eager to be a resource to the US Government wherever our organizational and member expertise can be of use. Attached, please find our response to this RFI.

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

To make the interagency regulatory process more transparent and accessible, USDA, FDA, and EPA could more clearly communicate *how* they work together to regulate biotechnologies, strengthened with examples of the regulatory process for specific products of biotechnology. Both the 2017 Update to the Coordinated Framework and The Unified Website for Biotechnology Regulation provide helpful information but leave ambiguity for the application of this information.

- The Coordinated Framework provides very useful examples of product areas and the agencies and offices with regulatory purview (Table 2) and provides an overarching description of how the agencies work together (Section E).
- The Unified Website for Biotechnology Regulation is a useful starting point for stakeholders who want to familiarize themselves with the Coordinated Framework and the laws, legislation, and guidance that are relevant to biotechnology innovation and regulation.

These resources offer little in describing how—or even if— the three agencies work together in practice for given technologies, or the path that a given biotechnology might take through and between agencies. Innovators may lack clarity on which agency they might need to work with first and regulatory timelines when multiple agencies are involved (e.g., whether agency review happens concurrently or consecutively). This type of information can help companies prioritize data collection to optimize review timelines and plan experiments for data collection efficiently. It might also

encourage regulatory agencies to work together more frequently, streamlining regulatory activities.[1] Making this type of information clear and upfront will have an outsized impact on academic researchers and start-ups that are inexperienced with the regulatory system. It will also be useful to scientists and the public more broadly, who have a stake in understanding this process.

Question 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.

Engagement with regulators:
Regulatory officials have publicly indicated their availability and willingness to speak with individuals and companies at any stage of the development of new biotechnologies. This is a tremendous benefit for stakeholders, and could be better emphasized on their websites, particularly with regards to early stage development. Agencies could individually—or even better, jointly—establish a formalized portal through which developers could request virtual appointments with an agency staff member, who would act as an early-stage regulatory point-person.[2] Crucial decisions are made early in the development of an engineered organism to optimize its biological activity or function. Developers may find out after expending significant resources to produce a given strain that a few differences, such as the use or removal of a given antibiotic, make a significant difference in the regulatory process. Expressing this openness to communication early in product development—even as concepts and approaches are designed and tested in academic labs—could help minimize confusion and enable developers to make informed decisions early in development. "The Future of Microbial Biotechnology: From Research to Regulation" workshop, held in February 2022, was incredibly useful both for increasing understanding of the regulatory ecosystem and also for expressing regulator availability for consultation. Indeed, the success of a regulatory approach that relies on "early and often" communication between regulators and developers hinges upon the dissemination of that approach to stakeholders and on the capacity of regulators to work with stakeholders in a timely, predictable, and transparent manner. Thus, it is crucial that regulatory agencies both publicly encourage engagement from the research community, potentially through the portal described above, and that they have sufficient staffing, expertise, and resources to meet this need. Ideally, data on consultation number and frequency would be documented so that trends and justification for additional staff can be made, as warranted.

Preparing for future biotechnologies:
Engineering biology research and advancements in scaling and manufacturing processes leave the bioeconomy poised for massive innovation and expansion. Recognizing that many new types of products will need regulatory review, the U.S. Government should support technically-based horizon scanning in coordination with regulatory agencies. This will enable these agencies to anticipate policy and regulatory clarifications and developments that will be needed over short, medium, and potential longer-term time horizons. At present, "first-in-kind" products have very long and arduous paths through the regulatory system, which can stifle the interest of researchers in pursuing novel products

[1] Hodgson, A., Alper, J., Maxon, M.E. 2022. *The U.S. Bioeconomy: Charting a Course for a Resilient and Competitive Future*. New York, New York: Schmidt Futures. https://doi.org/10.55879/d2hrs7zwc
[2] See Conclusion 6-6, National Academies of Sciences, Engineering, and Medicine. 2017. *Preparing for Future Products of Biotechnology*. Washington, DC: The National Academies Press. https://doi.org/10.17226/24605.

(see *The U.S. Bioeconomy: Charting a Course for a Resilient and Competitive Future*; pg 73). Horizon scanning can identify where advances in regulatory science are most needed and can inform policy review and clarification efforts to enable a more nimble, risk-based response when the biotechnology products of the future near commercialization. (See *Preparing for Future Products of Biotechnology*.)

Because the regulatory agencies are constrained by limited funding, it may be appropriate for Congress or the Administration to establish a Commission or other body to evaluate the Coordinated Framework and how it can be modified, streamlined, or even replaced to ensure efficient and appropriate regulatory actions and policies are in place. (See *The U.S. Bioeconomy: Charting a Course for a Resilient and Competitive Future)*

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

The Unified Website for Biotechnology Regulation could be strengthened by providing additional information to help stakeholders determine *which* agencies a biotechnology may be regulated by. This information exists for several product areas, for example, in Table 2 of the 2017 Update to the Coordinated Framework, and should be communicated on the Website.

Agencies could also consider the development of a web-based tool, perhaps similar to that used to determine disclosure requirements for bioengineered foods. Innovators could supply parameters such as product type, sources of genetic material, application area, etc., and receive information on the agencies and regulations that apply to their technology, contact information for taking next steps, and point to relevant laws, legislation and guidance. To avoid confusion and keep the information current with respect to developing technologies, agencies will need to consistently review and periodically update the Coordinated Framework (and be afforded the adequate resources to do so), as they are called to do in Section F of the 2017 Update. Such efforts require significant resources and expertise, which regulatory agencies must be given to ensure the continued development of a safe, secure, and productive bioeconomy.

Question 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.

As agencies develop and make plans to implement regulatory reforms, they should focus intently on clarity and agility. Regulations need to be clear to the innovators developing new products and clear to the consumer/customer base for those products, in addition to the public at large. Regulations need to be developed in recognition of the pace of technical advancement, and thus enable agile implementation. Agencies should work with public private partnerships to build and maintain connections to developing technical capabilities.

In addition to the consideration being given to new and emerging products of biotechnology, some areas of current regulation could be included in regulatory updates:

Plant-Incorporated Protectants: A 2020 proposed rule for "Exemptions of Certain Plant-Incorporated Protectants (PIPs) Derived From Newer Technologies" would have exempted from regulation PIPs that "pose no greater risk than PIPs that meet EPA safety requirements, and could have otherwise been

created through conventional breeding." A final decision on this rule would bring needed clarity. In finalizing that rule, EPA should consider the significant benefits that may be realized by exempting additional categories of PIPs, such as plant immune receptors (NLRs) from non-sexually compatible food crops. Such a move could enable faster response to the diseases that threaten our food supply and feedstocks of the entire bioeconomy.

Intergeneric microorganisms:
TSCA gives regulatory authority for "new" or "intergeneric" microorganisms to EPA. The Coordinated Framework clarifies that "intergeneric" includes microorganisms into which chemically synthesized DNA "that is not identical to that found in the subject genus" has been introduced. This seems to require 100% sequence identity between an introduced sequence and any sequence in the subject genus. It may be appropriate to reevaluate this standard. Small genetic changes made in a laboratory that are equivalent to those that could have occurred in nature—and that likely do exist in nature and are unknown because they haven't been sequenced—can be expected not to pose an outsized risk.

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

Researchers, start-ups, and others involved in early-stage product development may perceive the regulatory environment to be uncertain and/or prohibitive for new and emerging products, such as synthetic cells and cell-free systems. For example, MCANs must include information, such as taxonomic designation, that is challenging to apply to synthetic cells or cell-free systems. Clarification on how such technologies should prepare TERAs and MCANs would be useful. The "come talk to us" stance of regulators is laudable and appreciated; however, additional publicly available information on the application of regulations to emerging technologies would be beneficial, particularly to early-stage development.

As new solutions to challenging national and global needs are identified, it is important that the technologies with the greatest "benefit to potential negative consequence"-ratio are not unduly held back, delayed, or abandoned as a result of the regulatory process. Anecdotally, companies may deselect the most promising or most impactful technical capabilities in favor of technologies with fewer regulatory hurdles and greater regulatory certainty. Thus, every effort to align regulatory burden with actual risk should be pursued. Furthermore, the agencies should have sufficient funds or partnerships for horizon scanning activities that highlight coming regulatory needs (see question 2).

Question 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.

While USDA and FDA have important, on-going roles to play in the regulation of biotechnologies, EPA may see a wider range of new types of products of biotechnology for which it has regulatory authority under TSCA. These might include synthetic cells, cell-free systems, cells that transcribe non-canonical

nucleotides, organisms or systems with reassigned codons (either to canonical or non-canonical amino acids), etc. EPA may also see engineered microbial consortia being developed for use in agricultural soils, waterways, or elsewhere that remediate pollutants, control invasive species, or perform other functions. TSCA Sec. 725.155 refers to singular microorganisms when describing information that should be provided in MCANs. EPA could clarify required data for consortia: should an MCAN be submitted for each new microorganism in a consortium, and, if so, is any evaluation of the emergent properties of a consortium necessary?

Biocontainment strategies may be important for some of these environmental release applications. The lessons learned over decades of environmental release of genetically engineered plants and more recent biopesticides and biofertilizers should inform the development of standards for needed biocontainment measures for products with given characteristics.

Question 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?

- Short term: Regulatory agencies should prioritize accessibility of the regulatory system through attention to plain language needs and increased, direct engagement with the technical research community.
- Long term: The regulatory agencies and other stakeholders might evaluate whether or not the Coordinated Framework is the best approach to effective and efficient regulation moving forward. They should continually engage in horizon scanning activities to build understanding of coming technical capabilities through engagement with public private partnerships that engage with research and industry.