EBRC Engineering Biology Research Consortium

Regulatory Clarity, Communication, and Nimbleness: Enabling the safe and secure deployment of biotechnologies to address global challenges

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Technologies being developed today in academic, government, and industry laboratories are poised to usher in a biotechnology revolution that supports human, plant, and animal health and wellbeing; ensures global food security; and combats climate change. The United States is at the forefront of this revolution, and its regulatory agencies are and will continue to be tasked with establishing and enforcing rules and regulations that ensure the commercialization of biotechnologies that are viable and economically-sound solutions and do not present unacceptable risk. Stakeholders across the biotechnology ecosystem recognize and value the challenge of this role and respect the need for sensible regulation. However, real and perceived regulatory hurdles and uncertainty around future regulatory actions, can affect decisions by researchers and companies about which projects and products to pursue. Improved clarity, communication, and nimbleness of U.S. regulations will enhance innovation. The U.S. federal agencies responsible for regulating biotechnology need the resources and capacity to provide clear pathways to biotechnology regulation and effectively communicate them with stakeholders across the bioeconomy.

The modernization of regulations through the January 2017 Update to the Coordinated Framework for the Regulation of Biotechnology helped clarify the roles of Federal agencies, communication between agencies, and timelines for review of products of biotechnology. A 2019 Executive Order that addressed the regulation of agricultural products was also an important step. Now, the Biden Administration Executive Order on the bioeconomy represents an opportunity to "identify areas of ambiguity, gaps, or uncertainties" in relevant regulation and policy, which may occur in the regulations themselves and/or in the way those regulations are communicated or understood by the private sector. If regulatory agencies are able to deliver on this directive, they will enable the development of products that deliver maximal benefits to society while minimizing associated risks. We herein articulate select areas of uncertainty and concern that have caused challenges in the development of biotechnologies.

Clarity of coordination and regulation among U.S. agencies

USDA, EPA, and FDA should be commended for the development of The Unified Website for Biotechnology Regulation. This resource 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. However, it offers little in describing how the three agencies work together or the path that a given biotechnology might take through and between agencies. Visitors are instead directed to the websites of individual agencies and may lack clarity on which agency they might need to work with first, the types of data required by each, and/or how the timelines and coordination between agencies might work. The anecdotal reliance on consultants to help companies prepare for and navigate regulation highlights the lack of clarity within the system and represents another obstacle to the success of small-mid sized businesses.

To make the interagency regulatory process more transparent and accessible to stakeholders, the Unified Website could be expanded to provide: i) a summation of Section E of the 2017 Update to the Coordinated

Framework to describe *how* USDA, FDA, and EPA work together to regulate biotechnologies, strengthened with clarity and/or examples about how Working Groups and MOUs might, in practice, facilitate coordination around a single biotechnology product; and ii) information to help stakeholders determine which agencies a biotechnology may be regulated by. This could be as straight-forward as sharing Table 2 from the 2017 Update to the Coordinated Framework on the website. Alternatively, a decision tree could be useful, perhaps similar to that used to determine disclosure requirements for bioengineered foods. At the end of the decision tree, or as an addition to an adapted form of Table 2, the user could be directed to the relevant areas of agency websites and linked to information about the documentation that may be required. 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. To communicate that such a tool is meant to be a useful aid to stakeholders and not a definitive regulatory decision, users could be required to click a button acknowledging the non-binding nature of the decision tree before using it.

This enhanced communication and increased visibility into the regulatory process would inform researchers at all stages of development, from technology conceptualization to scaling and commercialization. This could also help early-stage entrepreneurs demonstrate to investors that the regulatory processes are not an insurmountable barrier.

EPA, USDA, and FDA: Communication of agency-specific regulatory approach and timelines

In addition to visibility into interagency regulatory processes, innovators would also benefit from greater visibility into the regulatory processes within EPA, USDA, and FDA. Each agency commendably provides extensive resources on their websites and point to the pieces of legislation that establish regulatory authority. It is less clear, however, which considerations might be wise for innovators to examine during development, which data and documentation are needed, what happens after paperwork is submitted, and how long review processes take. For example, EPA's website is incredibly useful for pointing to the rules and regulations that EPA uses to regulate products of biotechnology, however companies may struggle to understand how those rules and regulations *apply* to the products they are developing. It could be useful to develop a schematic or case study that represents the regulatory process with an example product. Such a schematic or case study would be most useful if it described or exemplified the ideal time to reach out to regulators, timelines, important considerations, and the data and documentation required. Minimally, the website might point readers to (and link directly to) specific sections of TSCA, FIFRA, and other relevant guidance documents. PDFs of rules and regulations might also be enhanced with links to referenced statutes. Any clarity that can be provided on these topics will be incredibly useful, particularly for small to mid-sized organizations taking their first products to market.

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 agency staff whose job it is to guide developers with early-stage questions. An agency staff member could then act as an early-stage regulatory point-person. 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 develop 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 could help minimize confusion within industry and enable developers to make informed decisions early in development. 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 manner. Thus, it is crucial that regulatory agencies have sufficient funding, staffing, and resources to meet this need.

Horizon scanning to promote a nimble regulatory system

Engineering biology research and advancements in scaling and manufacturing processes leave the bioeconomy poised for massive innovation and expansion. Recognizing that many 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. While the agencies cannot be bogged down by developing clear policy for technologies that may not exist for years to come, they can use the information generated through horizon scanning to identify where current policies, guidance, and regulations are insufficient or where there might be ambiguity in which agencies have regulatory purview. They might also recognize areas where current strategies for assessing biological risk are insufficient. That information can be incorporated into policy review and clarification efforts as opportunities arise and will enable a more nimble, risk-based response when the biotechnology products of the future near commercialization. (See *Preparing for Future Products of Biotechnology*.)

Conclusion

As regulatory agencies identify ambiguities, gaps, or uncertainties in biotechnology regulation and undertake the important work of providing clarity, communicating standards with stakeholders, and building agility into their processes, they will enable bioeconomy stakeholders to develop products with greater confidence in their understanding of the pathways to commercialization. If regulatory agencies are appropriately funded, staffed, and resourced, the U.S. Government can maintain and build upon its position of leadership in the global bioeconomy and address major societal challenges.