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Racing to Be First to Be Second

A bioeconomy that delivers environmental, economic, and social benefits requires a coordinated regulatory framework.

In laboratories and start-ups across the United States, a new era in biology is already changing the ways in which food, fuel, and materials can be produced. It's not hard to imagine neglected industrial hubs in the American heartland coming to life to produce biobased commodity chemicals from feedstocks grown on nearby farmland, creating jobs and reducing carbon emissions. It's a little harder to imagine over the horizon—where DNA-based data storage becomes a low-energy alternative to server farms, or biobased construction materials modulate temperature and moisture in homes and offices from Alabama to Alaska.

Making these visions a tangible part of American life will require a step change in how society approaches industry. As the authors of "Building a Bottom-Up Bioeconomy" in this journal put it: "Rather than trying to industrialize biology, the real task is biologizing industry." This means breaking with the centralized industrial practices of the past, superseding petroleum-based production processes, and rethinking models of manufacturing success to include regional and local supply chains. It also means changing governance and regulations that were created for the industries and products of the previous century, so that regulators can respond to new opportunities and risks as the bioeconomy evolves over the next one.

Racing to be first to be second

Biotechnology was born in California in the 1970s with the development of recombinant DNA. With federal support it has grown to be a driving force in many economic sectors, including agriculture, energy, and medicine. It generates at least 5% of US gross domestic product, according to the most recent estimates. Globally, the bioeconomy is predicted to be worth $4 trillion per year by the end of the decade.

Historically, biotechnologies in the United States have advanced faster than the laws and regulations that govern them, meaning that regulation can become a bottleneck. In 2012, the Obama administration prepared a National Bioeconomy Blueprint that prioritized creating an efficient regulatory system. The blueprint called for improvements to "reduce barriers, increase the speed and predictability of regulatory processes, and reduce costs while protecting human and environmental health." At that time, it was already clear that federal safety assessment pathways for future products, such as ready-to-cook genetically engineered salmon, lacked clarity and could not serve the more complex regulatory challenges ahead.

However, progress building a new regulatory system has been sluggish. Last year, the President's Council of Advisors on Science and Technology (PCAST) identified "regulatory uncertainty" as one of three key gaps that are slowing the country's progress in advancing the bioeconomy. This uncertainty is a "significant hurdle for companies with novel, complex, and often transformative ideas and products." It can be felt all over the nascent bioeconomy today. At a recent National Academies of Sciences, Engineering, and Medicine (NASEM) workshop on biomanufacturing, one participant described companies "racing to be first to be second" as the approval pathways are often clarified only after a pioneer's innovation triggers a confusing cascade of responses from multiple agencies, costing that first mover time and money—and potentially survival.

Without clear safety assessment pathways for the regulatory decisions that determine whether new products can be marketed, some entrepreneurs have taken promising ideas—including goats that produce milk that may curb diarrhea in children—abroad or abandoned them altogether. Regulatory confusion at this scale can also have a damaging effect on public confidence in both the nascent industry as well as the government's ability to regulate it.

As a scientist and biotechnology advocate who has worked in this space for decades, I am concerned that this failure to

create appropriate governance forfeits the opportunity to build the kind of bioeconomy that best serves society. As Debra J. H. Mathews, Rachel Fabi, and Anaeze C. Offodile II have written in *Issues*, a "framework for governance of developing technologies should intentionally drive toward societal benefit, instead of simply hoping it emerges from the market." Creating jobs, a cleaner environment, and other desirable outcomes requires intention and a regulatory process that incentivizes both good products and good manufacturing processes. Today, however, a confusing tangle of legacy rules and agency jurisdictions stymies greater progress for public good.

Trying to build a future on a legacy from 1986

Governance of today's bioeconomy rests on the legacy of decisions made more than three decades ago. Specifically, in 1986, when the US government sought to create a regulatory framework in response to emerging genetic engineering tools, "it retrofitted old laws under a plan called the Coordinated Framework for the Regulation of Biotechnology," according to futurist Amy Webb and geneticist Andrew Hessel, instead of crafting new laws to govern genetically engineered products. Statutes written decades before genetic engineering became possible were reinterpreted to accommodate the regulation of new technologies that were then in their infancy.

This overall approach resulted in a decentralized regulatory process that relies on agencies coordinating themselves via a voluntary framework. The coordinated framework tasks three primary agencies—the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA), and the Department of Agriculture's (USDA) Animal and Plant Health Inspection Service (APHIS)—with regulating the products of biotechnology.

In addition to the three key agencies, other federal regulatory agencies and offices are also tasked with the oversight of certain products of biotechnology, including the USDA's Food Safety Inspection Service, the Department of the Interior's Fish and Wildlife Service, the Commerce Department's National Oceanic and Atmospheric Administration, and the Department of Labor's Occupational Safety and Health Administration. The result for developers of new types of products is often confusion, lack of coordination, and ambiguous jurisdiction.

In 2017, NASEM sounded a warning regarding the lack of regulatory transparency. Its report, *Preparing for Future Products of Biotechnology*, observed that "public confidence in government oversight of emerging technologies may be eroded" in the absence of mechanisms that provide clarity and transparency for how the regulatory process is conducted.

That same year, the EPA, FDA, and USDA updated the coordinated framework. The update provided an outline of regulations that may apply to biotechnology products and guidance to navigate the regulatory process within each agency. However, the framework lacks guidelines to help companies determine which agency or agencies have jurisdiction over their product or its components. And even so, agency roles and responsibilities can remain ambiguous.

Federal oversight of genetically engineered and, more recently, genome-edited crops and animals illustrates the unintended consequences of a decentralized regulatory process that depends on "regulatory triggers" as defined by each agency's statutory remit. Sometimes more than one of the three regulatory agencies has oversight, for different reasons, for a single product.

The coordinated framework requires, for example, that USDA's APHIS decides whether a crop should or should not be regulated under the Plant Protection Act. If APHIS determines that the crop does not pose a plant-pest risk, USDA requires no further oversight. However, if that crop contains a biopesticide or "plant-incorporated protectant," a second regulatory agency, the EPA, is tasked with reviewing only the pesticidal protein and gene under the Federal Insecticide, Fungicide, and Rodenticide Act and the Federal Food, Drug, and Cosmetic Act. The EPA does not review the crop itself—only whether the available data demonstrate that the biopesticide component does not pose unreasonable risks to human health, nontarget organisms, and the environment. A third regulatory agency, the FDA and its Center for Food Safety and Applied Nutrition, then engages in a voluntary consultation with the manufacturer to determine whether the agency has any further questions regarding the manufacturer's assessment of the crop's food safety. For innovators attempting to bring their products to market, this can add years to the approval process.

The case of two lab-grown mosquitos

This perplexing system can have a chilling effect on bringing a product from the lab to market, and it can privilege market entrants that happen to choose one pathway arbitrarily over another. A case in point can be seen in the differing experiences of two novel mosquito control methods, Oxitec and MosquitoMate, as they went through the regulatory process.

Both treatments involved the development of mosquitos grown in labs, and both were designed to slow the transmission of mosquito-borne diseases such as malaria, dengue, and Zika by reducing mosquito populations. And both products presented the US regulatory system with a type of product that it had not encountered before. However, Oxitec had developed its mosquito with genetic engineering, while MosquitoMate did not: its mosquito was infected with a bacteria called *Wolbachia*. An article in *Pathogens and Global Health* described the very different regulatory pathways that the two products encountered.

Although both products used altered mosquitos whose impact outside the lab could not be fully known, they met different regulatory fates. Using an established path for the testing of pesticides, it took MosquitoMate approximately six years to be reviewed, tested, and approved for market by the

EPA. In contrast, for nearly 10 years, the Oxitec product went from the USDA, to FDA, to EPA before Oxitec withdrew its application.

The authors write that compared to MosquitoMate's relatively straightforward path to approval, Oxitec's "decade-long struggle to field test OX513A demonstrates the complexity, unpredictability, and opacity of current technology governance." In particular, the authors noted, this governance system, which lacks methods to adequately gather public input, is "ill-equipped to manage controversy."

Moving innovation out of labs and into the world

If the United States is to realize the ambitions of President Biden's new National Biotechnology and Biomanufacturing Initiative to expand domestic biomanufacturing and foster innovation across the nation, action is needed to develop a transparent, fully staffed regulatory system that is prepared for future products of biotechnology. Without that, many discoveries will remain mainly in laboratories and fail to advance a more sustainable economy.

After the 2017 *Preparing for Future Products of Biotechnology* report, which was sponsored by the FDA, USDA, and EPA, NASEM published *Safeguarding the Bioeconomy* in 2020, funded by the Office of the Director of National Intelligence. In October 2021, the philanthropic initiative Schmidt Futures, where I work, convened a special task force to inform a report called *The US Bioeconomy: Charting a Course for a Resilient and Competitive Future*. All three reports converged on a set of actions to streamline the regulatory process, improve interagency communication, and fund and train agencies so that they can anticipate future products of biotechnology.

There are several approaches that could help in the short term. For example, setting a deadline of, say, 90 days after submission to designate a lead agency for each product's regulatory review would make the process more efficient for applicants to navigate. Another improvement would be to enable agencies to assess risks in parallel rather than sequentially, so that review processes do not drag on as long as they did with Oxitec.

Another possible strategy for agencies is the use of enforcement discretion when a new product is considered low risk. For example, the FDA recently made its first enforcement discretion decision for "slick-haired," genome-edited beef cattle, determining that the edit did not raise any safety concerns. This strategy may permit developers to bring technology products to market more efficiently without compromising animal or human safety. And as long as the decisionmaking process is transparent and can adequately integrate public input, it can also build public trust.

Finally, agencies are under-resourced and lack both funding and staff to prepare for the proliferation of new products now and in the future. There is an immediate need to prepare a new cohort of experts to scan the horizon for future biotechnology products, especially for those that are the first of their kind. There will also be a need for technical advice on the data that agencies will need to evaluate regulatory approval applications for products of emerging biotechnologies. Meeting these needs will require a multidisciplinary, targeted training program for regulatory staff involved in oversight and commercialization of emerging biotechnology products.

Biocoordination

In the short term, the highest priority issues for the agencies to address are communication and collaboration among themselves. The CHIPS and Science Act of 2022 mandates the formation of a National Engineering Biology Research and Development Initiative to be supported by an Initiative Coordination Office (ICO). This ICO could support and coordinate the National Biomanufacturing and Biotechnology Initiative.

This bioeconomy ICO—if established by the White House Office of Science and Technology Policy—could facilitate interagency collaboration, cross-train regulators, and provide for needed horizon-scanning. The bioeconomy ICO could coordinate training opportunities for regulators and facilitate an information network to link regulators with industry, academia, and others relevant to the bioeconomy and its products. The ICO could also coordinate regular agency collaboration on horizon-scanning for future products of biotechnology, and it could work to establish a single point of entry for biotechnology products through which product developers could enter and be guided through the regulatory system. These last two actions alone could address two important bottlenecks in the current system.

To tackle the thorny problem of improving trust in the regulatory process, the federal government could convene a commission—bringing together experts from industry, government, and academia—to inform updates to regulatory statutes that better reflect modern biotechnologies. This kind of forum would be the ideal space to tackle the complexities of the pre-commercialization phase, which require a delicate balance for regulators between transparent decisionmaking and confidentiality obligations.

Concerted and deliberate policy action will be required to turn today's nascent biomanufacturing industry into a dynamic engine of growth and sustainability. From where we stand now, it's hard to anticipate precisely how this technology may transform the economy, the environment, and American life. Surely, the process will require a twenty-first-century governance and regulatory framework that can simultaneously manage complex data-based decisions and foster public trust as the sector evolves.

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