Managing the Risks of Biotechnology Innovation

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Workshop Policy Paper

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Biotechnology Governance in a Time of New Risks and Opportunities

The benefits of biotechnology are tangible and obvious to the world. COVID-19 vaccines have saved millions of lives, and CAR-T cell therapies are bringing the concept of personalized medicine to successful cancer treatment. Beyond the medical applications of biotechnologies, it is common to have biological enzymes in laundry detergents for stain removal, plant-based "meats" in burgers that "bleed," and direct-to-consumer genetic testing ancestry services. These biotechnology advances are not just the result of sustained biological research and hard work by scientists around the world, but also the convergence of advances in computing, machine learning, and the accessibility of powerful research tools that accelerate discovery, allowing important scientific questions to be asked and answered. These sustained advances have influenced consumer expectations, and will lead to more biotechnology products used in everyday life.

However, there are also risks to biotechnological progress. Even in the early days of recombinant DNA technologies, it was understood that there were inherent risks in understanding biological mechanisms, as that improved understanding could be used to cause harm. Accidents are also possible if some biotechnology product "escapes" from containment, causing harm to people, animals, or the environment. In response to the potential safety concerns of this new field, a group of scientists, government officials, and journalists met at California's Asilomar Conference Center in 1975 to discuss the possible risks of manipulating genetic material and to declare a moratorium on the work until safety questions were methodically addressed. Fortunately, there was little cause for the specific safety concerns that spurred the meeting, and biotechnology as a field rapidly progressed. Different conceptions of the risks of biotechnology development, however, did lead to divergent national governance approaches—especially regarding genetically modified organisms (GMOs)—as well as different oversight mechanisms for biological research that involved manipulating genetic material. Those divergent governance mechanisms persist for the regulation of laboratory research and the fielding of GMO crops.

Now, with synthetic biology tools like CRISPR, which allows for precise gene editing and gene-synthesis technologies, biotechnology is a more powerful and accessible technology than ever before. Biotechnology is also a truly international endeavor, practiced in laboratories and companies around the globe, complicating the implementation of any governance mechanism that could prevent or mitigate misuse. Nations have evolved their own systems to govern laboratories and biotechnologies, and there is no one place at the international level that harmonizes those different approaches. Still, it

remains important to examine how responsible governance could be achieved and to advance the development of workable governance systems to prepare for biotechnology developments in the coming years. While recent advances in science and technology have been amazing—demonstrated in the rapid scientific response to SARS-CoV-2—the apex of biotechnological use and understanding is far off. While it is now possible to "read" and "write" DNA, using that genetic language for "expression," particularly of new functions important for engineering biology, remains a work in progress. Understanding the language of DNA still requires considerable research and development, trial and error, and basic research.

A great deal is not yet understood about the natural world, such as infectious diseases that afflict animals, plants, and humans and the responses to those pathogens by the human immune system. The function of many genes is still difficult to know just by looking at the genetic sequence. In 2016, J. Craig Venter and colleagues published a "minimal bacterial genome," which was a pared-down version of *Mycoplasma genitalium*, containing only those genes essential for life. To date, the functions of many of these "essential genes" are unknown. When the omicron variant first started causing a rapid rise in COVID-19 cases in the winter of 2020–21, researchers observed that the omicron variant was significantly different from the delta variant in its sequence. Yet how those differences translated into actual differences in transmissibility or clinical impact was impossible to determine until cases of illness could be observed; they could not be reliably predicted.

The fact that there is much to learn about biology should be a source of optimism and a call to action. The foundations for governance built now could have lasting and beneficial influences on the future trajectory of biotechnology so that its advantages are realized while minimizing risks.

Summary of CFR Workshop

The Council on Foreign Relations held a virtual workshop on November 7, 2022, titled "Managing the Risks of Biotechnology Innovation." The workshop was divided into two parts: the first focused on the risks and benefits of biotechnologies, and the second on potential governance mechanisms, though there was considerable overlap in both sections.

- *Governance of biotechnology is not a simple "guns, gates, and guards" problem.* It is not possible to wall off biotechnologies to prevent their misuse or to hold information related to biotechnology secret. There are fundamental differences between biotechnology and other powerful technologies that require different approaches for governance to realize the benefits to health, agriculture, and other sectors. Further, in contrast to controlled weapons materials, for example, new potential biological threats could emerge from nature at any time.
- *There are benefits that biotechnology can theoretically bring, but those benefits will not evolve naturally; there will need to be a considerable effort and investment to make those benefits a reality.* A proliferation of biotechnologies could lead to some favorable, fundamental changes that can address scarce resources, such as vaccines. Climate change also poses new challenges that biotechnology can begin to address. However, the fact that biotechnologies have the potential to address pressing issues such as vaccine scarcity or crops affected by climate change does not necessarily mean that biotechnologies will be used that way by their funders and practitioners. Hoping that investments in

biotechnology will lead to improvements is not enough without active direction. The fact that resources have not traditionally been applied to pressing problems that biotechnology can address spurred the creation of the Coalition for Epidemic Preparedness Innovation in 2017, which fosters public-private partnerships to develop vaccines for MERS-CoV, Nipah, and Lassa viruses. Without a strategic goal to direct investments in helpful directions, biotechnology companies and their investors will fill already-profitable niches, which could not be the most beneficial for society in the long term.

Part of this problem of development can be addressed by calculating the full savings of investing in biotechnology products. Products such as fuel or specialty chemicals could be more expensive when made with biotechnology than products made using traditional approaches, such as petroleum-based methods. But that higher cost for biology does not factor in the potential benefits inherent in biotechnology products including sustainability, reduced logistic costs and environmental damage, and potential national security benefits of avoiding supply-chain shocks. Calculating the full costs and benefits of biotechnology products can provide a more realistic measure of the potential benefits of biotechnology applications that could encourage long-term investments.

- *The financial incentives and disincentives that affect biotechnology governance need to be squarely acknowledged.* One report estimates the market valuation for biotechnology will cross $950 billion by 2027, with agriculture-targeted biotechnologies estimated at $45 billion in 2020, growing annually at nearly 10 percent. Letting financial decisions alone affect governance in biotechnology is risky, but countering economic forces will require investment. Any controls or limitations on biotechnologies imposed by governments or international agencies will need to be designed with profit in mind, or they will be entirely ignored.
- *The benefits and risks of biotechnologies should be examined through a "One Health" lens.* One Health is an approach to health that recognises the interconnection between people, animals, plants, and their shared environment. While the concept of One Health is broadly acclaimed and uncontroversial, breaking down the stovepipes that have separated the health of people, animals, plants, and the environment has been exceptionally challenging. The fact that SARS-CoV-2 emerged from an animal infection and that 75 percent of emerging pathogens have been the result of animal "spillovers" is reason enough to alter course and take One Health more seriously. Beyond the risks of animal spillovers, however, there are also benefits to considering peoples' health along with animal health. There are pharmaceutical products for humans and for animals, and there could be vaccines for animals that directly benefit humans (vaccinating mice to prevent Lyme disease, for example). There could be synergies where investing in governance mechanisms can benefit both human and animal health, for example, in ongoing research to identify and attribute the source of illegal wildlife-trade animals or to identify the source of illegal timber. The potential for surveillance and other mechanisms to attribute misuse is an area for governmental investment, and investments in attribution can serve as a deterrent.
- *Expertise is critical when designing governance mechanisms.* Inappropriately developed governance mechanisms have led to poor outcomes or limited benefits of biotechnology such as seen with stem cell technologies and restrictions on the use of GMOs. While technical expertise is not the only ingredient for success in governance, it is a critical one. Donald A. Frederickson, the former head of the National Institutes of Health during the recombinant DNA debate in the 1970s remarked that

> "one of the most important lessons to be learned about controversy over use of high technologies . . . is the absolute requirement for expert opinion." Even more significant than general scientific expertise is the requirement for specific domain expertise in the area for which governance mechanisms are being developed. The amount of technical knowledge required to understand the implications of new virology research, for example, makes it challenging even for scientists in distinct disciplines (such as immunology, microbiology, chemistry, synthetic biology, epidemiology, or infectious disease medicine) to evaluate research outside their expertise. Without the nuance and long experience of people who have followed the progression of the field up close, it would be hard to avoid missing potential areas where governance can be usefully applied or mistaking smaller risks as potentially catastrophic risks, just because the mitigating details were unable to be absorbed by untrained ears.

Though there are no all-encompassing global governance mechanisms in biotechnology, there are multiple institutions and organizations that form an imperfect web of global governance. Many products that use biotechnology are highly regulated, such as medicines and therapies, diagnostic tests, and food, so producers target the development and manufacturing of biotechnology products to adhere to those requirements. Numerous regulatory agencies function as the Food and Drug Administration does in the United States. Organizations such as the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use bring regulatory agencies from the United States, Europe, Japan, and dozens of countries together to harmonize approaches to measuring toxicity or carcinogenicity, manufacturing, or measuring efficacy.

The World Health Organization (WHO) has often assembled scientists and interested stakeholders to develop norms for biotechnologies, including a framework to govern human germline editing (i.e., permanent genetic changes that can be passed down to offspring). A report from an expert advisory committee provides recommendations for other governance mechanisms for the technologies globally, but also at the regional, national, and institutional level. The same approach of convening experts and stakeholders to develop norms has been taken for a variety of biotechnology governance gaps, from the highly technical and uncontroversial (e.g., the manufacturing, licensing, and controlling of blood products and related in vitro diagnostic tests) to the use of artificial intelligence in health, or determining the origin of novel pathogens. When needed, the WHO will offer specific guidance about the safety of specific research techniques, such as how to perform research safely on SARS-CoV-2 virus. There is also an international committee that specifically approves individual experiments for variola virus, the causative agent of smallpox.

WHO does not typically engage on the topic of deliberate biological misuse or biological weapons, though they do have an expert independent advisory body to advise on health security matters. Biological weapons are outlawed by the 1975 Biological Weapons Convention (BWC), and while the staff to the convention, called the Implementation Support Unit, has done heroic work over the years to increase transparency, gather scientific expertise, and promote universalization of the treaty, there have been only three staff members. At the 2022 Review Conference, after considerable diplomatic efforts, that number has finally been increased—to four. (By comparison, the technical secretariat for the Chemical Weapons Convention has more than five hundred staff members). UN Security Council Resolution 1540 (2004) requires nations to adopt legislation preventing the proliferation of biological

(as well as nuclear and chemical) weapons and means of delivery, and establish appropriate domestic controls. In addition to these measures, there are also export controls on many of the potential pathogens which have been—and could be—weaponized, and organizations like the Australia Group, which harmonizes export control restrictions on those pathogens in its forty-two member countries.

Regulating access to biological pathogens is challenging by nature. With the exceptions of variola virus (smallpox) or 1918 influenza, most pathogens that have been previously weaponized, including *Bacillus anthracis*, the causative agent of anthrax disease, or *Francisella tularensis*, which causes tularemia, are found in the wild and routinely cause disease in animals and humans all over the world. The advent of synthetic biology tools makes regulating access to pathogens even more challenging. Using gene synthesis tools, the genetic material encoding pathogens can be chemically synthesized (or ordered from a company that specializes in synthesizing long stretches of genetic material), and the genetic code can be "booted up" in a laboratory. Though theoretically there is no limit to any pathogen being laboratory created in this fashion—in 2010, J. Craig Venter and colleagues made headlines when they created the first synthetic bacterial cell—it is still astoundingly complicated and error prone to create bacterial cells "from scratch." In contrast, the de novo synthesis of small viruses is listed as one of the most pressing biodefense risks by a 2018 report from the National Academies of Sciences, Engineering, and Medicine. Though there is considerable variety in the genomic size of viruses, they are generally smaller than bacteria.

The possibility to regulate gene synthesis technologies has been explored since the early days of synthetic biology tools, but gained salience in 2006 after a reporter from the *Guardian* ordered a small piece of the genetic material encoding smallpox from a gene synthesis company, demonstrating lax controls on a technology that could be misused. Since then, an industry organization called the International Gene Synthesis Consortium was formed that included most leading gene synthesis companies, where all agree to screen their orders and customers for potential security issues. The United States has also issued guidance for gene synthesis providers. Though screening orders can be automated and there is commercially available software to do so, it still requires interpretation from an expert, and thereby operational costs. To address this tax on responsible companies, California recently passed AB 1963, which requires many research institutions in California to only order gene synthesis products from companies that screen their orders for potentially fraudulent or dangerous orders. Similar legislation is being considered at the federal level. At the international level, the Nuclear Threat Initiative is working to establish an International Biosecurity and Biosafety Initiative for Science, which is intended to reduce emerging biological risks associated with technology advances, and which will take on gene synthesis technologies as its first task.

Main Gaps in Global Governance

The main gaps in global governance stem from the nature of biotechnology development itself, the lack of organization in response to misinformation and disinformation that undermines the development of biotechnology, and neglect of biosafety due to underfunding.

- *The speed of biotechnology development requires that flexible processes be put into place, to develop governance norms and identify "rules for the road."* Prospectively regulating biotechnologies with clear

rules that are useful to practitioners will be challenging. One risks irrelevance, for example, by banning a technique that is not used, or encompassing a greater swath of research than is practical or necessary. This happened when the Intelligence Reform and Terrorism Prevention Act of 2004 restricted activities with variola virus using vague language, which led to concerns that working with highly related and commonly used viruses like vaccinia (the vaccine strain for variola) would be treated equally harshly under the law. Prospective governance mechanisms could also close off potential benefits or applications of biotechnology that are currently unknown. To address this rapidly changing technical environment, a standard playbook should be used to gather domain-specific experts in the science and related technology along with interested stakeholders by an independent, respected party (e.g., WHO, National Academies, InterAcademy Partnership, or a technical body) to identify areas of common agreement and to identify rules of the road for further biotechnology development. This process of gathering and evaluating expert input takes time, but this process should be frequently used to better understand and reduce technical risks. Incentivizing the sharing of information internationally about biotechnology developments is also important.

- *Misinformation and disinformation can shape the progress and governance of biotechnology.* Well-funded groups have undermined the development of various biotechnologies, as seen in "golden rice," which was developed in the 1990s to combat vitamin A deficiency. However, this intervention has not been deployed due to unjustified safety concerns, and millions of children have died from vitamin A deficiency. Misinformation about GMOs, vaccines, and therapies is common, and has intensified during the COVID-19 pandemic. In addition, Russia has recently presented the presence of public health laboratories in Ukraine as cause for suspicion of misuse of biotechnologies. Sometimes institutions, newspapers, or research groups will organize to counter specific threads of misinformation and disinformation, but it is a significant, often uncompensated, obligation for those involved.
- *Biosafety is often underfunded, around the world.* At heart, biosafety is an occupational health consideration. Efforts to ensure that a worker in a poorly funded clinical laboratory receives training and personal protective equipment will help to raise safety standards in other types of laboratories as well. There are multiple international organizations and regimes that have a connection to promoting biosafety, including the WHO, but an underutilized tool is the newly developed International Organization for Standardization (ISO) Standard Biorisk management for laboratories and other related organisations. Regulatory bodies, scientific journals, and diplomatic scientific engagement should use the ISO standard as a global floor for biosafety management.

Prioritize Institutional Reforms to Address Future Threats

In order to address future threats, the United States needs to maintain a leadership role in international biotechnology innovation and governance. This role includes broader commitments, such as expanding support for international governance and funding and studying biosafety, as well as more specific actions such as expanding gene-synthesis screening.

- *The United States needs to remain a leader in biotechnology.* While there are certainly benefits of leading in biotechnology for economic growth, job creation, and the development of useful products, another benefit of leadership is the furthering of biotechnology governance norms. Given how

quickly biotechnology evolves, governance mechanisms will need to be developed through convening experts and interested stakeholders. If the United States wants to lead the conversation to shape an emerging biotechnology or scientific field and its rules—for example, what safety measures should be deployed, or what level of testing is required—it will need to be a leader in that biotechnology.

- *The United States should expand its support for international governance and harmonization efforts.* When the United States supports the WHO, the BWC, Australia Group, and other international technical harmonization groups, the ability of those organizations to shape governance norms, deter misuse, and prevent accidents is strengthened. Biotechnology is inherently international and cannot be controlled by any international command and control system. Building a web of governance, with multiple institutions and organizations shaping the rules of the road, is the only possibility for governance.
- *The United States should expand gene-synthesis screening to more countries and more companies.* The United States should make screening a priority for partner nations and take steps so that only screened orders are allowable for purchase in the United States. Screening orders will not remove the threat of laboratory-created pathogens that could be used as weapons, but it will add security and may be a deterrent to misuse.
- *Biosafety should be a national problem and should be funded and studied.* Often, biosafety is not perceived as important enough to afford resources dedicated to training, oversight, equipment, standards, and other costs that can detract from the funding of the research itself. The ISO standard for biorisk management is a good place to start, but there should also be laboratory accident reporting as well as technical studies in applied biosafety to determine how the field of biosafety can advance, what biosafety measures are necessary, and how laboratory work can be made as safe as possible.

Conclusion

Biotechnology is a broad field that shows tremendous promise for the future, but there is also the potential for risks stemming from accident or deliberate misuse. Attention to governance mechanisms to shape norms should be a priority for governments, scientists, and other stakeholders. However, governance should not only focus on the potential for harm. Benefits could go unrealized if there is only a focus on addressing risks and letting benefits occur only as market forces allow. A strategy is needed to identify the benefits that should be realized, and the potential risks that need to be mitigated to achieve those ends.

While biotechnology has advanced at an incredible pace over the last several decades, there is still a great deal that is unknown, and much left to discover. The foundations for governance built now could still have lasting, potentially beneficial influences on the future trajectory of biotechnology so that its benefits are realized while minimizing risks.