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Synthetic Biology

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The Technology Factsheet Series was designed to provide a brief overview of each technology and related policy considerations. These papers are not meant to be exhaustive.

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Executive Summary

Synthetic biology (sometimes referred to as "SynBio") is broadly defined as the application of engineering principles to biology, and in practice, refers to emerging technology that allows living organisms to be modified to serve user-defined purposes. While traditional biotechnology involves the transfer of smaller amounts of genetic material from one biological species to another, synthetic biology will permit the intentional construction of an entire organism.[1] It has the potential to allow scientists to design living organisms distinct from any found in nature and to redesign existing organisms to have novel or enhanced qualities.[2] The use cases of synthetic biology range from developing new therapeutics and vaccines for infectious disease to manufacturing novel biomaterials, biosensors, and biofuels. As scientists better understand biological systems, the potential applications of SynBio are anticipated to expand in scale and scope.

The continued growth of the bioeconomy—defined as the "production, utilization and conservation of biological resources, including related knowledge, science, technology, and innovation, to provide information, products, processes and services across all economic sectors"—is giving space for synthetic biology technology to become a more significant part of the overall economic landscape.[3] As with any technology that has a high potential for impact, SynBio presents a variety of pronounced opportunities, as well as risks. As the technology continues to mature and the number of market-ready applications grows, it is important for policymakers to consider how to promote the large number of opportunities the technology presents in the space of health and medicine, energy production, environmental recovery, food production, and more, while simultaneously protecting the public from foreseeable negative implications and risks, such as weaponization, consumer safety, and ecological stability.

Since synthetic biology bears significant similarities to previous biotechnology research on genetically-modified organisms and recombinant DNA, existing regulations in the United States place the majority of synthetic biology products into the current biotechnology regulatory framework. As SynBio becomes more prominent though, it will be important for regulatory schemes to uniquely target the technology and its implications beyond those captured through biotechnology frameworks. Policymakers must continue to engage in the progression of the technology, understanding how regulation and governance must evolve to ensure the public can realize the opportunities, while being protected from the risks.

1 Mandel, Gregory N., and Gary E. Marchant. "The Living Regulatory Challenges of Synthetic Biology." Iowa Law Review, 2014. https://ilr.law.uiowa.edu/print/volume-100-issue-1/the-living-regulatory-challenges-of-synthetic-biology/.

2 Ibid.

3 2018 Global Bioeconomy Summit. "Global Bioeconomy Summit Communique." April 20, 2018. https://gbs2018.com/fileadmin/gbs2018/Downloads/GBS_2018_Communique.pdf

What is Synthetic Biology?

Synthetic biology is a scientific field that incorporates biology, chemistry, computer science, and engineering to build biological systems with abilities that they inherently lack in nature. More broadly, it can be viewed as redesigning biological systems to perform a specific task with a user-defined purpose (for example, the production of a molecule or antibody, or novel bioremediation processes), or even to recreate a living system.[4] The inclusive nature of this definition means that that synthetic biology can be applied to the creation of new organisms or biological systems to fill numerous needs and purposes.[5] The overarching goal of SynBio is to make the engineering of biological systems faster, cheaper, and more predictable, while maintaining robust and safe development practices. Although many of the goals laid out by the development community have been achieved, there is still work to be done on speed, predictability, and the cost of human capital.[6]

At the core of engineered organisms are synthetic biological circuits that execute the tasks of sensing inputs, processing logic and performing output functions. The creation of these new systems is defined by a "design, build, test, learn" (DBTL) cycle drawn from traditional engineering disciplines.[7] The process focuses on the understanding that DNA sequences can act as building blocks, and can be assembled together to produce a living entity with any desired combination of traits, much like how someone can assemble a car by constructing a system comprised of many individual (and uniquely functional) parts. It can be applied to, at a simpler level, introduce or modify a single gene to, at a more complex level, creating the genome of an organism *de novo*.

At a high level, the outcome of a DBTL cycle is to create a product—and in the case of SynBio, an engineered biological system. The cycle consists of defining an intended output, or what is to be designed and created; predicting how to build the output by drawing on biological knowledge and foundations, as well as growing computational models with applied machine learning and biological design; testing the output of the design and build phases; and finally, learning from observed results of the output, and modifying the process to run another cycle iteration, if needed.

The DBTL process is aided by numerous foundational technologies. First, is **DNA synthesis technology**, which advanced over the past several years to allow for the synthesis of increasingly long stretches of DNA *de*

4 National Human Genome Research Insitute. "Policy Issues in Genomics: Synthetic Biology". Available online. https://www.genome.gov/about-genomics/policy-issues/Synthetic-Biology

5 Presidential Commission for the Study of Bioethical Issues. "New Directions: The Ethics of Synthetic Biology and Emerging Technologies." December 2010. https://bioethicsarchive.georgetown.edu/pcsbi/synthetic-biology-report.html

6 DARPA ISAT. "Synthetic Biology Study." 2003. http://dspace.mit.edu/handle/1721.1/38455

7 National Academies of Sciences, Engineering, and Medicine. 2018. *Biodefense in the Age of Synthetic Biology*. Washington, DC: The National Academies Press. https://doi.org/10.17226/24890.

novo enabling the ability to produce significant amounts of artificial DNA.[8] Individually synthesized stretches of DNA can be linked together using **recombinant DNA technology**, allowing for the creation of longer (chromosome and genome length) synthetic DNA constructs.[9] This process of linking allows for the construction of multiple genes that act together to produce a desired biological function. The DNA that is synthesized and recombined can be **DNA sequenced** in order to confirm that it is what the researcher designed.

While the above represent the base technologies for creating a synthetic DNA segment, additional technologies are critical for introducing the segments into organisms. **Genome editing** allows a break to be made in an organism's genome to allow the synthetic DNA to be integrated as a specific point. Meanwhile, **viral delivery technologies** allow researchers to utilize viruses to introduce a synthetic DNA sequence to an organism.

Technological Limitations

There exist significant limitations to synthetic biology currently, and research is ongoing to expand the applications and scalability of synthetic biology technologies. Synthetic biology is limited by the relatively small number of microbes or plants used and our current knowledge of how specific genetic elements act in combination. Research is ongoing to expand the number of organisms that can be used for various applications. Additionally, the business-to-business synthetic biology market works to reengineer existing microbes to do their job better (for example, redesigning the organism to produce more of a specific molecule). This research is helping to solve the scalability problem of synthetic biology.

Current Applications and Market Development

Synthetic biology, while emerging, underpins the creation of the bioeconomy and could prove to be an extremely disruptive technology, with many positive applications.[10] Currently, genetically engineered organisms and other synthetic biology products account for 2% of the U.S. economy.[11] Industrial biotechnology, which now incorporates several types of synthetic biology, is a broad field that impacts numerous sectors of the economy, including food and agriculture, energy and climate, manufacturing and chemicals, and health and medicine.

8 Hughes, Randall and Ellington, Andrew. "Synthetic DNA Synthesis and Assembly: Putting the Synthetic in Synthetic Biology". *Cold Spring Harb Perspect Biol.* January 9, 2007.

9 Ibid.

10 Bueso, Tensi and Tangney, Mark. "Synthetic Biology in the Driving Seat of the Bioeconomy." *Trends in Biotechnology*, May 2017.

11 Carlson, Robert. "Estimating the biotech sector's contribution to the U.S. economy." *Nature Biotechnology*, March 2016.

Table 1. Sectoral uses of synthetic biology

Food and Agriculture	Energy and Climate	Chemicals and Manufacturing	Health and Medicine
• Genetically engineered plants and animals • Food additives • Cell-based meats	• Biofuels • Bioremediation • Carbon technologies	• Chemicals • Plastics	• Vaccines • Drugs and medicines • Protein therapeutics

Food and Agriculture

Genetically modified plants and animals are the best-known synthetic biology products and advances in synthetic biology will only increase the different abilities that can be added to plants. An popular example of this technology is Impossible Foods, a meat alternative food producer, uses a synthetic biology-based cellular system to produce a protein that makes their meat alternatives "taste like meat".[12] Other meat alternatives that are cell-based, rather than plant-based, are being developed and are popularly known as meat in a petri dish.

Additionally, numerous food additives that change the flavor, appearance, and nutritional value of foods are produced using synthetic biology. Overall, advances in the food and agriculture space use synthetic biology to make food production less resource intensive and more environmentally friendly, as well as to provide alternatives to conventional foods.

Energy and the Environment

Energy production, remediation, and climate change could see synthetic biology solutions developed in the coming years. Significant investment in generating biofuels from algae and other microorganisms spurred several advances in this technology and demonstrate the potential for major advances in energy and power production. Additionally, the use of engineered organisms to clean oil spills and other contaminants demonstrated to potential uses of synthetic biology products for bioremediation. Scientists also point to using synthetic biology to remove carbon from the atmosphere as a way to combat climate change, though these technologies remain years from the market. Ultimately, the SynBio presents the opportunity to change the landscape of energy consumption by making it more distributive in nature. This distributed model, as compared to the current centralized model, supports efforts for climate change, energy accessibility, and more.

Manufacturing and Chemicals

Scientists and industry are developing synthetic biology approaches to produce chemicals, textiles, drugs, and plastics. For example, SynBio can be used for the production of fatty acids that are not produced in

12 Heme + The Science Behind Impossible. Impossible Foods. Available online. https://impossiblefoods.com/heme/

nature, such as branched chain, odd chain, or with specific functionality that can be used in developing cleaners, lubricants and oil field chemicals.[13] Additionally, numerous companies operate in the business-to-business synthetic biology space. These companies build organisms for other companies to use or reengineer microbes currently in use to do their job better (for example, redesigning the organism to produce more of a specific molecule).

Health and Medicine

Synthetic biology allows scientists to push the current boundaries of disease treatment even farther. CAR-T cells, recently given approval by the FDA, represent a first-in-class treatment using a patient's own cells to fight cancer. Additional engineering enabled CAR-T cells to target cancer cells more accurately, increasing their value as a therapy. Advances in protein production and design technologies could improve the production of therapeutic antibodies (and other proteins, such as insulin), including those used in cancer immunotherapy and antiviral therapeutics such as ZMapp, the Ebola-fighting therapy.

Synthetic biology applied to vaccine design led to the development of new types of vaccines and sped the development of vaccine candidates, including those for Zika virus and the 2019 coronavirus. Further research identified ways in which the microbiome (bacterial communities that live within us) can be engineered to treat metabolic diseases and potentially immune diseases (such as Crohn's disease and colitis). Advances in synthetic biology are opening new doors to the treatment of human disease, and protecting people from the very risks people associate with SynBio weaponization. Through the rapid development of targeted diagnostics, therapeutics, and vaccines, applications of the technology in the healthcare space could protect against novel biorisks.

Expansion of Research & Applications

New applications for synthetic biology emerge constantly, with newly identified processes enabling the development of new applications. For example, while some anti-cancer therapies (CAR-T cells) worked extremely well against some cancers, they could not be used against others. Scientists expanded the application of this technology by creating a new circuit (Notch-gated CAR-T cells) that allows for better targeting of the cancer.

Scientists are also expanding frontier technologies, particularly those that will allow the creation of living organisms. Recent advances at the frontier included the making a bacterium with entirely artificial DNA.

13 "Application of Synthetic Biology in Chemicals Industry." Applications of Synthetic Biology in Chemicals Industry. Accessed 2020. https://www.genscript.com/chemicals-industry.html.

Market Landscape

Advances in synthetic biology are stemming from the private, public, and academic sectors. Some of the major private-sector players for bioproducts, biofuels, healthcare, and food products include **Amyris Biotechnologies**, **Codexis**, **Genecor**, **Life Technologies**, **Genomatica**, **Qteros**, **CODA Genomics**, **OPX Biotechnologies**, **Modular Genetics**, and **Impossible Foods**.[14] There are many startups emerging in the SynBio space, though, demonstrating a lower-barrier of entry for potential innovators. Further, it demonstrates the clear interest from private funding schemes, such as venture capital (VC) firms, to invest in the development and deployment of the technology: In the U.S. alone, over $12 billion has been invested in SynBio technology over the last decade, $4 billion just in the last year.[15]

In early 2020, the U.S. Department of Defense's **Manufacturing Innovation Institute (MII)** released a notice of intent to begin research and development in the field of synthetic biology.[16] Many universities including Harvard University, Massachusetts Institute of Technology (MIT), Stanford University, Johns Hopkins University, University of Maryland, and many more are also contributing largely to the research and development of synthetic biology applications.

Due to the relatively low barrier of entry for some synthetic biology development and application, there has been an emergence of "do it yourself" (DIY) labs and actors across the world.[17] This adds to the innovation landscape, though it poses unique questions for effective oversight and governance.

14 "Current Uses of Synthetic Biology." BIO. Accessed 2020. https://archive.bio.org/articles/current-uses-synthetic-biology.

15 Kirk, David. "Investing in Synthetic Biology: a View from Synbio Markets." BioSpace. BioSpace, January 8, 2020. https://www.biospace.com/article/investing-in-synthetic-biology-a-view-from-synbio-markets/.

16 "Department of Defense Releases Notice of Intent for Synthetic Biology Manufacturing Institute." Department of Defense Releases Notice of Intent for Synthetic Biology Manufacturing Institute | Research Development, December 10, 2019. https://researchdevelopment.vpr.virginia.edu/department-defense-releases-notice-intent-synthetic-biology-manufacturing-institute.

17 Talbot, Margaret, Oliver Sacks, and Hannah Fry. "The Rogue Experimenters." The New Yorker, May 18, 2020. https://www.newyorker.com/magazine/2020/05/25/the-rogue-experimenters.

Current Governance and Regulations

Currently, the regulation of synthetic biology is concentrated at the federal level, being governed under existing regulations for biotechnology more generally. Internationally, countries rely similarly on legislation for genetically modified organisms (GMO).

U.S. Federal Regulation

Federal regulation of biotechnology, including emerging synthetic biology applications, is governed by the **Coordinated Framework for Regulation of Biotechnology**, overseen by the Office of Science and Technology Policy (OSTP).[18] The Coordinated Framework establishes roles for the U.S. Department of Agriculture (USDA) via the Animal and Plant Health Inspection Service (APHIS), the Department of Health and Human Services (HSS) via the Food and Drug Administration (FDA), the Centers for Disease Control (CDC), and the National Institutes of Health (NIH), and the Environmental Protection Agency (EPA) in regulating genetically engineered organisms.[19]

Federal oversight of synthetic biology under the Coordinated Framework focuses on concerns related to environmental protection, consumer safety, and biosecurity. This regulation is designed to regulate the product, not the scientific process of generation, under the doctrine that biotechnology itself is not harmful, but certain products may be.[20] This structure evolved over the years to include emerging biotechnology products, including those created using synthetic biology.

Environmental protection

The EPA regulates all intergenic microorganisms (including bacteria, fungi, algae, viruses, protozoa, etc. that are formed by combining material from organisms in different genera) used for commercial purposes, classifying microorganisms made with synthetic DNA as "new chemical substances". This regulation excludes microorganisms used for academic research. The APHIS regulates the import, movement, and release of genetically modified organisms that contain plant pest DNA or were made using a plant pest as a vector.

18 Office of Science and Technology Policy. "Coordinated Framwork for Regulation of Biotechnology." June 26, 1986. Accessed via APHIS, available online. https://www.aphis.usda.gov/brs/fedregister/coordinated_framework.pdf

19 National Academies of Sciences, Engineering, and Medicine. Preparing for Future Products of Biotechnology. Washington (DC): National Academies Press (US); 2017 Jun 28. 3, The Current Biotechnology Regulatory System. Available from: https://www.ncbi.nlm.nih.gov/books/NBK442204/

20 Office of Science and Technology Policy. "Modernizing the Regulatory System for Biotechnology Products: Final Version of the 2017 Update to the Coordinated Framework for the Regulation of Biotechnology." Accessed via EPA, available online. https://www.epa.gov/sites/production/files/2017-01/documents/2017_coordinated_framework_update.pdf

Consumer safety

The FDA regulates modified organisms that are used to produce drugs, food, food additives, dietary supplements, or cosmetics. In particular, the FDA oversees all genetically modified animals, under the premise that the introduction of foreign DNA is a "new animal drug".[21] One key aspect of FDA regulation is ensuing that any product falling under its regulation, including most synthetic biology products, conforms to the FDA's Good Manufacturing Practices, thus ensuring it meets safety standards for human use.[22]

Biosecurity

Biosecurity regulations are enforced by the CDC and APHIS and are focused on preventing the use of a certain number of high-risk pathogens known as Select Agents. This effort is aided by the "Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA", which prevents companies from synthesizing long stretches of DNA from select agents without applying strict "know your customer" rules. Additionally, certain pathogens cannot be synthesized, such as smallpox.[23]

Specific regulatory authorities include:

- **NIH Guidelines on Recombinant DNA:** Establishes guidelines for NIH-funded research using recombinant or synthetic DNA in order to minimize risks to the user and the risk of accidental release. Applied to most federally-funded research.
- **Toxic Substances Control Act (EPA):** Allows the regulation of microbes with synthetic DNA in order to prevent the release of harmful microbes into the environment.
- **Plant Protection Act (APHIS):** Allows regulation by APHIS of plants altered with DNA derived from plant pests or using plant pests as a vector.
- **Federal Food, Drug, and Cosmetics Act (FDA):** Allows regulation of any modified organism that is used as or produces a human or animal drug, food, food additive, dietary supplement, or cosmetic. Allows regulation of any animal with synthetic DNA by classifying that DNA as a "new animal drug".
- **Public Health Security and Bioterrorism Preparedness Response Act (CDC/APHIS):** Allows for the regulation of Select Agents, which are defined as organisms or toxins that pose a severe threat to public, animal, or plant health and safety. Regulations prevent the synthesis of DNA sequences derived from Select Agents.

21 Ledford, Heidi. "FDA ready to regulate transgenic animals." *Nature*: January 2019.

22 Carter, Sarah R., Rodemeyer, Michael, Garfinkel, Michele S., and Friedman, Robert M. *Synthetic Biology and the U.S. Biotechnology Regulatory System: Challenges and Options*. United States: N. p., 2014. Web. doi:10.2172/1169537.

23 Enserink, Martin. March 11, 2005. "Unnoticed Amendment Bans Synthesis of Smallpox Virus." *Science* 307(5715): 1540-41. DOI: 10.1126/science.307.5715.1540a

- **Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA (HHS):** This guidance prevents companies from synthesizing long stretches of DNA from select agents without applying strict "know your customer" rules. Additionally, it restricts certain pathogens from being synthesized, such as smallpox.

- **National Science Advisory Board for Biosecurity:** Though not a regulatory act, the National Science Advisory Board for Biosecurity (NSABB) is a federal advisory committee that addresses issues related to biosecurity and dual use research. The NSABB is comprised of members with a broad range of expertise including molecular biology, microbiology, infectious diseases, biosafety, public health, veterinary medicine, plant health, national security, biodefense, law enforcement, scientific publishing, and other related fields.[24]

International Regulation

The **European Union**, the **United Kingdom**, **China**, **Singapore** and various other nations similarly approach the governance of synthetic biology through the lens of existing biotechnology frameworks.[25]

The **Biological Weapons Convention (BWC)** was the first multilateral disarmament treaty banning the development, production and stockpiling of an entire category of weapons of mass destruction: namely, bioweapons. Under current standards, the BWC would apply to any form of SynBio weaponization.[26]

Public Purpose Considerations

As synthetic biology grows in applications, usage, and accessibility, significant public purpose considerations will arise. The regulatory focus on products over process both protects the independence of the scientific community and creates an opportunity for dual-use research to arise.

- **National R&D Strategy:** The U.S. is currently leading in synthetic biology research and development, but other nations, such as those in the European Union, as well as Singapore and China, are heavily investing in the technology to boost their economies and capitalize on the opportunities for the national defense, energy, health, and agriculture sectors.[27] When exploring the governance and regulatory landscape, it is important to consider how the U.S. can maintain its competitive advantage, while still allocating attention and resources to effective oversight and risk-focused regulation of SynBio R&D. This is especially important because advances in synthetic biology could prove beneficial in national defense schemes, should there novel biothreats arise.

24 "National Science Advisory Board for Biosecurity (NSABB)." National Institutes of Health. U.S. Department of Health and Human Services. Accessed 2020. https://osp.od.nih.gov/biotechnology/national-science-advisory-board-for-biosecurity-nsabb/.

25 Trump, Benjamin D. "Synthetic Biology Regulation and Governance: Lessons from TAPIC for the United States, European Union, and Singapore." *Health Policy* 121, no. 11 (2017): 1139–46. https://doi.org/10.1016/j.healthpol.2017.07.010.

26 "Biological Weapons—UNODA." United Nations. United Nations. Accessed 2020. https://www.un.org/disarmament/wmd/bio/.

27 Gronvall, Gigi Kwik. "US Competitiveness in Synthetic Biology." *Health Security* 13, no. 6 (2015): 378–89. https://doi.org/10.1089/hs.2015.0046.

- **Workforce Training**: Related to the idea of U.S. competitiveness is the concept of workforce training. A finite number of workers in the United States use biology or biological techniques on a regular basis. This will lead to a potential skills gap as synthetic biology drives the bioeconomy forward. It is important for policymakers to consider how these gaps could be filled, and how to build a steady pipeline of trained workers.

- **Dual-Use Research:** The weaponization of SynBio a foreseeable risk, and one that is potentially heightened by the democratized nature of the development of the technology. National governments must consider how to mitigate dual-use risks in order to support the production of overwhelmingly beneficial technology and deter the production of harmful technology.

- **Regulatory Gaps:** Due to their unique characteristics, certain synthetic biology products, such as genetically modified plants that were not made with the use of a plant pest, are currently not regulated by a specific authority. Switchgrass engineered to be a more efficient feedstock for biopower, for example, is not regulated by the APHIS because it is not a plant pest, nor was it made using a plant pest.[28] It is important for policymakers to consider how synthetic biology fits under current regulation frameworks, and where there may be room (and a defined necessity) for additional, targeted regulation.

- **Regulatory Burden**: As more synthetic biology products are brought to the market there will need to be an increase in the ability of regulatory agencies to handle the increased workload. For example, from 1998-2012, the EPA received less than two applications per year, on average, for experimental release of engineered microbes; in 2013 alone, the EPA received seven applications for experimental release of engineered microbes.[29]

- **Cost and Accessibility:** Current synthetic biology-based therapies, such as T cells engineered to fight cancer, are some of the most expensive medical therapeutics available (costing approximately $450,000 per patient)[30]. Will the cost of synthetic biology products, particularly in the health and medicine field, create new tiers of medical access?

- **Scalability:** The scalable production of synthetic biology products is vital to its ability for impact. Both technical scalability and operational scalability are important factors. Policymakers should consider how resources and infrastructure could help support the issue of scalability, both for public sector and private sector production.

- **Democratization:** Organizations such as iGEM provide repositories of DNA building blocks that could be easily assembled in a DIY manner, allowing the development of synthetic biology products outside of a laboratory setting.[31] Democratization of production poses both opportunities and risks. A lower-barrier of entry to engage with the technology could allow for more opportunities for innovation, and allows for increased access to the products themselves. It may be important to consider how DIY labs should be considered in both local and federal regulatory schemes, especially as it pertains to oversight and safety.

- **Consumer Knowledge**: As more synthetic biology products are developed for the marketplace, particularly in the food and agriculture sector, there may be increasing pressure for labelling rules. This leads to important questions of whether

28 Pollack, Andrew. "By 'Editing' Plant Genes, Companies Avoid Regulation." *The New York Times*. January 1, 2015.

29 Carter, Sarah. "Synthetic Biology and the U.S. Biotechnology Regulatory System: Challenges and Options." *Presentation.* J. Craig Venter Institute. https://sites.nationalacademies.org/cs/groups/pgasite/documents/webpage/pga_152546.pdf

30 Kolata, Gina. "This Treatment Can Cure Cancer. Can It Mend the Heart?" *The New York Times.* September 17, 2019.

31 Vavitsas, Kostas. May 18, 2018. "Biosecurity: Do synthetic biologists need a license to operate?" PLOS Synbio Community. Accessible online at https://blogs.plos.org/synbio/2018/05/18/biosecurity-do-synthetic-biologists-need-a-licence-to-operate/

synthetic biology products are any different from non-synthetic products (Are the means of product more or less safe?), and how much consumers should know about what they are purchasing and what information should be required to be disclosed.

- **Public Acceptance:** Related to consumer knowledge is the consideration of public acceptance. In order for various sectors to benefit from the application of synthetic biology, consumers must be willing to accept the technology. It is important for investors, developers, and policymakers alike to consider what would encourage the acceptance of SynBio technology by the broader public.

- **Security & Safety:** Synthetic biology products create new avenues for the creation of bioweapons, including pathogens and toxins. Beyond generating currently regulated organisms and toxins, synthetic biology could be used to make existing pathogens and toxins more dangerous or, eventually, to create a new pathogen that is not found in nature.

- **Biodiversity:** Synthetic biology could be used to bring back extinct species or increase the reproductive ability of certain species, impacting biodiversity. While increasing biodiversity is not thought to be a negative impact of synthetic biology, it poses questions about how decisions to reintroduce a species of change the makeup of a community should be made. There is also a concern that synthetically developed organisms could outcompete their natural competitors or disrupt ecosystems. It is important to consider how this disruption could negatively impact a region's biodiversity.

- **Containment:** Once released into the environment, it is unclear the extent to which synthetic biology products will be able to be prevented from replicating or propagating synthetic genetic elements within naturally occurring organisms. Scientists, for example the Safe Genes group at the Department of Defense, are working on solutions to issues of containment.[32] Some technical approaches to containment include the production of a genetic firewall through genome recoding and physical containment of microbes using auxotrophies (inabilities of an organism to synthesize a particular organic compound required for its growth), regulation of essential genes, and expression of toxic genes.[33] Though there are approaches that are being developed and testing, it is important to consider how regulation and oversight plays a role in the effect governance of synthetically created organisms, especially as it pertains to their release and containment.

32 "Defense Advanced Research Projects Agency." Defense Advanced Research Projects Agency. Accessed 2020. https://www.darpa.mil/program/safe-genes.

33 Stirling, Finn, and Pamela A. Silver. "Controlling the Implementation of Transgenic Microbes: Are We Ready for What Synthetic Biology Has to Offer?" *Molecular Cell* 78, no. 4 (2020): 614–23. https://doi.org/10.1016/j.molcel.2020.03.034.

Appendix: Key Questions for Policymakers

National R&D Strategy

- How can the U.S. stay competitive in the research and development of synthetic biology?
- Should the public sector play a role in the promotion of market development? If so, how should this role be defined within the larger landscape of private sector investment and development?
- How does the development of the bioeconomy play a role in the large U.S. innovation landscape, especially as policymakers consider modern national competitiveness strategies?

Workforce Training

- Does the United States have the life science education and training capacity to facilitate the development of the bioeconomy? How will the U.S. expand its current workforce pipeline in order to support growth in the SynBio field?
- As alternative, bio-based forms of production are pursued across all industries, what plans are in place for dealing with job loss in the traditional industries (for example, traditional meat production being replaced by plant- and cell-based meat alternatives)?

Regulatory Approach

- How can regulation act as a promoter for foreseeable opportunities? What is the balance between oversight and encouragement, to ensure there is domestic progress of SynBio technology? How can regulation support the growth of necessary infrastructure, resources, and tools for to capture the opportunities of SynBio?
- What are current and foreseeable governance gaps of SynBio as it is currently regulated under the biotechnology framework?
- Do regulators have sufficient capacity to meet the increased need for oversight of products produced with synthetic biology?
- Will an increase in personalized therapeutics and treatments dramatically increase the burden on health regulators to appropriately govern consumer products? If so, how should this be addressed?

Cost & Accessibility

- How can new SynBio technologies impact the developing world? What role should various domestic and international actors play in ensuring the low-cost and accessible nature of these technologies?

Dual-Use Research

- Does dual use research suggest that there should be greater regulation of the scientific process, as opposed to specific products?

- What steps can be taken to prevent scientists from engaging in high-risk dual use research, especially if they do not rely on federal funding?

Democratization

- What opportunities are presented through the democratization of synthetic biological production and application? How can a regulatory framework acknowledge and support these opportunities?

- What are the governance needs around DIY biologists, if any? How can governance structures, if needed, be built to support the positive aspects of democratized biological innovation, while addressing potential risks?

- Will DIY biologists be liable for any damage that they cause (to health, the environment, etc.) as a result of accidental release or inappropriate use of their products?

Consumer Knowledge

- Should all synthetic biology products made available to consumers be required to be labelled as being produced via synthetic biology? Is labelling necessary if there is no demonstrated risk to the consumer from any given product?

Biosecurity

- How can we prevent individuals from making pathogens more dangerous? And how can we detect and prevent against engineered pathogen release?

- Are current sequence-based methods of identifying dangerous synthetic DNA sequences sufficient for preventing the synthesis of the most high-risk pathogens?

Biodiversity

- Should there be any requirements for community outreach and approval before introducing an engineered species to a community?

- Should we bring back species simply for the sake of biodiversity or should they serve a "useful purpose"?

- How could the introduction new, and reintroduction of old, species impact and/or disrupt present ecosystems and biodiversity? Are there ways to mitigate undesirable disruptions? How can we account for uncertainty of outcome?

Containment

- What technologies are being put into place to ensure that organisms that are accidentally released can be contained? How do we test the efficacy and readiness of these technologies?

- Does containment need to be considered after a product is used for its intended purpose, for example a biological or food product that is excreted?

- Is there a need for environmental monitoring to survey for the presence of synthetic biology products that may be accidentally released?