Bold Goals for U.S. Biotechnology and Biomanufacturing

Harnessing Research and Development to Further Societal Goals

MARCH 2023

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Bold Goals for U.S. Biotechnology and Biomanufacturing

Harnessing Research and Development to Further Societal Goals

Per Executive Order 14081

Compiled by

The White House Office of Science and Technology Policy

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U.S. Department of Energy

U.S. Department of Agriculture

U.S. Department of Commerce

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Introduction

The world is on the cusp of an industrial revolution fueled by biotechnology and biomanufacturing. Emerging biological technologies are and will continue to transform the foundation of our physical world – everything from clothing, to plastics, to fuels, to concrete. Through biomanufacturing, sustainable biomass across the United States can be converted into new products and provide an alternative to petroleum-based production for chemicals, medicines, fuels, materials, and more. While the most prominent applications today are related to human health, biotechnology and biomanufacturing are expanding to build products that will be everywhere in our lives and support climate and energy goals, improve food security, and grow the economy across all of America. Our Nation's bioeconomy – economic activity derived from biotechnology and biomanufacturing – is strong. However, maintaining our global leadership in research and development (R&D) and reaping the full benefits of the bioeconomy requires more action from across the public and private sectors.

On September 12, 2022, President Biden signed an Executive Order (E.O.) on "Advancing Biotechnology and Biomanufacturing Innovation for a Sustainable, Safe, and Secure American Bioeconomy." In the E.O., the President laid out his vision for a whole-of-government approach to advance biotechnology and biomanufacturing by creating a research agenda that outlines the foundational and use-inspired R&D needs that will lead to innovative solutions in health, climate change, energy, food security, agriculture, supply chain resilience, and national and economic security. The E.O. also launched a National Biotechnology and Biomanufacturing Initiative to ensure that, beyond R&D, we have the domestic capacity to make in the United States all the bio-based products that we invent here. This will create new jobs, build stronger supply chains, and contribute to our climate goals.

The President's E.O. calls on Federal departments and agencies to harness biotechnology and biomanufacturing innovation to further societal goals and transform industries related to: (1) climate change solutions, (2) food and agriculture innovation, (3) supply chain resilience, (4) human health, and (5) cross-cutting advances. This document includes five sections responsive to the E.O., individually authored by the Department of Energy (DOE), Department of Agriculture (USDA), Department of Commerce (DOC), Department of Health and Human Services (HHS), and National Science Foundation (NSF), respectively, with input from other Federal departments and agencies.

Bold Goals for U.S. Biotechnology and Biomanufacturing R&D

Each of the five sections presents bold goals that highlight what could be possible with the power of biology. These goals are intended to provide a broad vision for the U.S. bioeconomy and what can be achieved with concerted action from industry, academia, nonprofits, the Federal Government, and other organizations. The bold goals set ambitious national targets for the next two decades to help establish R&D priorities that will be critical to advance the bioeconomy. They are not meant to represent commitments by an agency or department to undertake specific activities. Each section also outlines the essential R&D needed to achieve these bold goals for the U.S. bioeconomy, opportunities for public-private collaboration, and recommendations for enhancing biosafety and biosecurity. Underpinning all this work is the Administration's commitment to growing the U.S. bioeconomy safely, ethically, and equitably.

Achieving these goals will require significant prioritization of R&D investments and other efforts across the U.S. government, as well as actions from the private sector; state, local, and tribal governments; and international partners. Although a single agency or department is the lead author of each section, advancing the bold goals in each sector will require efforts from multiple agencies and departments, as shown in Appendix A. In the upcoming months, the White House Office of Science and Technology

Policy will lead the development of a strategy and implementation plan to execute on R&D priorities and other actions identified in this report.

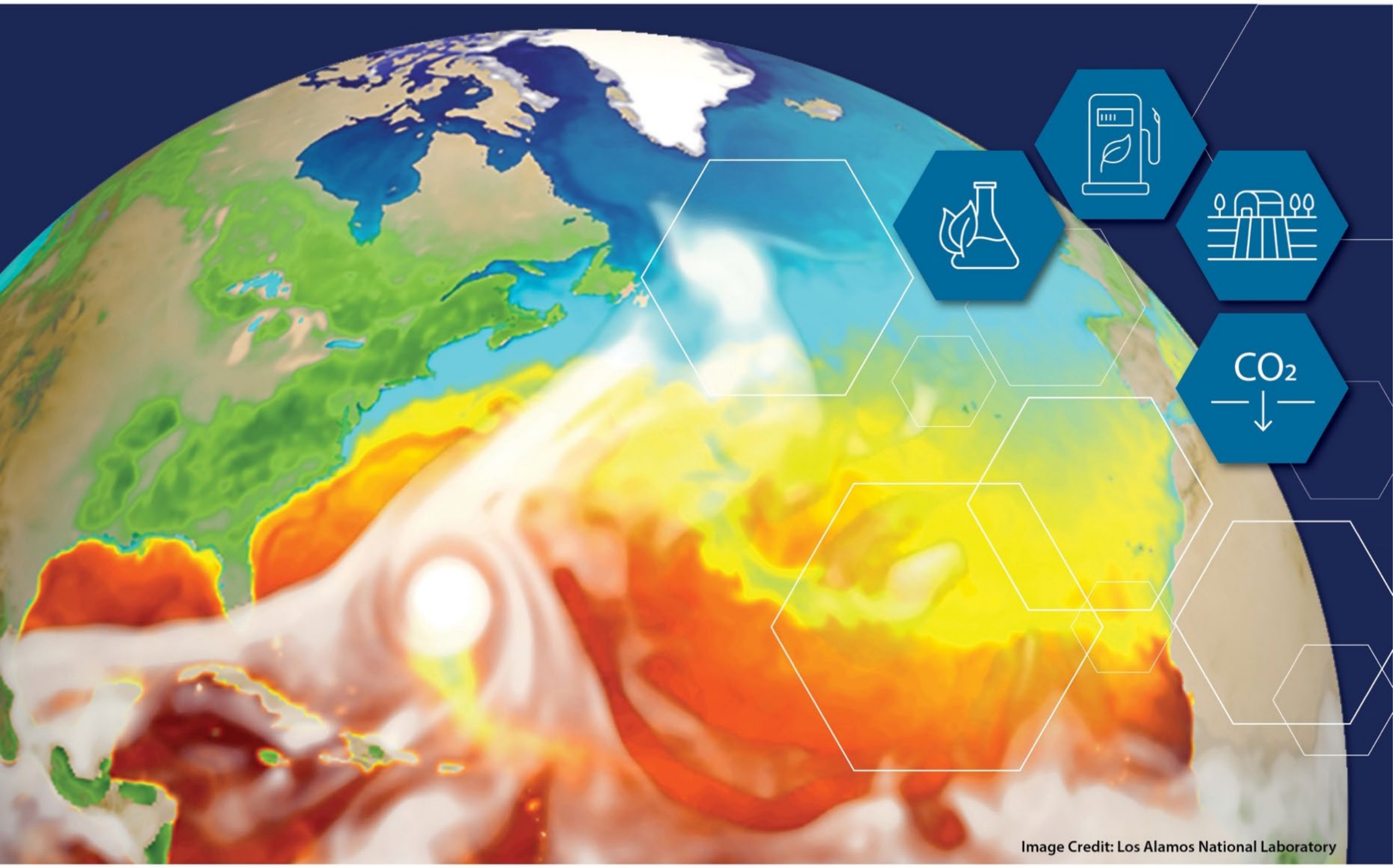
Bold goals for the U.S. bioeconomy include, for example:

- **Climate:** In 20 years, demonstrate and deploy cost-effective and sustainable routes to convert bio-based feedstocks into recyclable-by-design polymers that can displace more than 90% of today's plastics and other commercial polymers at scale.
- **Food and Agriculture:** By 2030, reduce methane emissions from agriculture, including by increasing biogas capture and utilization from manure management systems, reducing methane from ruminant livestock, and reducing methane emissions from food waste in landfills, to support the U.S. goal of reducing greenhouse gas emissions by 50% and the global goal of reducing methane emissions by 30%.
- **Supply Chain:** In 20 years, produce at least 30% of the U.S. chemical demand via sustainable and cost-effective biomanufacturing pathways.
- **Health:** In 20 years, increase the manufacturing scale of cell-based therapies to expand access, decrease health inequities, and decrease the manufacturing cost of cell-based therapies 10-fold.
- **Cross-Cutting Advances:** In 5 years, sequence the genomes of one million microbial species and understand the function of at least 80% of the newly discovered genes.

Reaching these bold goals will require progress in other areas beyond R&D to ensure that innovation can lead to safe, effective, and equitable products in our daily lives which grow the bioeconomy across all of America and with our partners globally. In forthcoming reports and plans, departments and agencies will outline recommendations and steps that are underway to advance the following:

- Data for the bioeconomy – establishing a Data Initiative to ensure that high-quality, wide-ranging, easily accessible, and secure biological data sets can drive breakthroughs for the U.S. bioeconomy.
- Domestic biomanufacturing infrastructure – expanding domestic capacity to manufacture all the biotechnology products we invent in the United States and support a resilient supply chain.
- Workforce development – growing training and education opportunities for the biotechnology and biomanufacturing workforce of the future.
- Regulatory clarity and efficiency – improving the clarity and efficiency of the regulatory process for biotechnology products to help ensure products come to market safely and efficiently.
- Biosafety and biosecurity – creating a Biosafety and Biosecurity Innovation Initiative to reduce risks associated with advances in biotechnology and biomanufacturing.
- International engagement R&D – pursuing cooperation through joint research projects and data sharing, while mitigating risks and reaffirming democratic values.

These "Bold Goals for U.S. Biotechnology and Biomanufacturing" align with other recent Administration actions, such as the National Biodefense Strategy, the Executive Order on America's Supply Chains and resultant 100-Day Review, the Net-Zero Game Changers Initiative, the American Pandemic Preparedness Plan, the National Strategy on Hunger, Nutrition, and Health, and the Cancer Moonshot, among others. Furthermore, the recent CHIPS and Science Act unlocks new R&D opportunities, spurs regional innovation, and advances workforce development in biotechnology and biomanufacturing. All these actions support the growth of the American bioeconomy and bolster the R&D needed to fully harness biotechnology and biomanufacturing to build on our Nation's unique strengths of innovation, agricultural and biomass production, and entrepreneurship.



Biotechnology and Biomanufacturing R&D to Further Climate Change Solutions

In collaboration with other U.S. Federal Government departments and agencies, this report was authored by the U.S. Department of Energy

Executive Summary

Transforming the U.S. economy to achieve net-zero greenhouse gas (GHG) emissions by 2050 will necessitate major advances across many economic sectors. To meet this transformational goal, action is needed now to spur focused research and development (R&D) that translates innovations in bioscience and biotechnology to broad scale implementation to mitigate the effects of climate change.

This report on climate change solutions provides an overview of ten bold goals and associated R&D needs to safely harness rapid developments in biotechnology and biomanufacturing to dramatically decrease GHG emissions, increase carbon sequestration, and develop innovative products. Achieving these goals in partnership with the private sector will help mitigate the effects of climate change and contribute to a strong and resilient bioeconomy with multiple benefits across broad geographic regions and socio-economic strata within the United States.

These bold goals for climate solutions are cross-cutting and will require efforts across the U.S. government and the private sector. The ten bold goals are grouped into four themes where biotechnology can play a critical role in reducing GHG emissions and removing carbon from the atmosphere.

Theme 1 addresses the need to develop more carbon-neutral **transportation and stationary fuels** by expanding renewable feedstock availability and producing more sustainable aviation and other strategic fuels. New ways to produce such fuels are needed to shift the United States from fossil-based fuels toward renewable liquid fuels, which will likely still be required by a subset of transportation and other applications currently difficult to electrify.[1]

Theme 2 seeks alternative processes to produce **chemicals and materials** from renewable biomass and intermediate feedstocks by developing low-carbon-intensity product pathways and promoting a circular economy for materials. Achieving these goals will position the United States at the forefront of a vibrant global bioeconomy while producing net-zero or net-negative emissions, reducing use of and reliance on fossil fuels, and increasing use of recyclable-by-design chemicals and materials like bio-based products.

Theme 3 seeks to develop **climate-focused agricultural systems and plants** and includes bold goals to develop restorative and resilient feedstock production systems, engineer better plants tailored as bioeconomy feedstocks, improve usage of current feedstocks, and engineer more efficient protein production systems. These efforts will generate a variety of biomass feedstocks with increased resilience, yield, and nutrient use efficiency, laying the foundation for the expanding U.S. bioeconomy.

Theme 4 addresses **carbon dioxide (CO_2) removal.** The goals within this theme expand landscape-scale biotechnology solutions to store carbon within soils and enable biomass to remove and store carbon. Implementation of these solutions will dramatically increase CO_2 removal from the atmosphere across whole ecosystems through landscape-scale carbon sequestration and management techniques.

[1] The U.S. National Blueprint for Transportation Decarbonization | U.S. Departments of Energy, Housing and Urban Development, and Transportation, and U.S. Environmental Protection Agency

Bold Goals for Harnessing Biotechnology and Biomanufacturing

The following goals for climate change solutions provide a broad vision for the U.S. bioeconomy but are not commitments by the U.S. Department of Energy (DOE) to undertake specific activities. Achieving these goals will require significant prioritization of R&D investments and efforts across the U.S. government, as well as actions from the private sector and state, local, and tribal governments.

Theme 1: Transportation and Stationary Fuels

Goal 1.1: Expand Feedstock Availability – In 20 years, collect and process 1.2 billion metric tons of conversion-ready, purpose-grown plants and waste-derived feedstocks and utilize >60 million metric tons of exhaust gas CO_2 suitable for conversion to fuels and products, while minimizing emissions, water use, habitat conversion, and other sustainability challenges.

Goal 1.2: Produce Sustainable Aviation Fuel (SAF) – In 7 years, produce 3 billion gallons of SAF with at least 50% (stretch 70%) reduction in GHG lifecycle emissions relative to conventional aviation fuels, with production rising to 35 billion gallons in 2050.

Goal 1.3: Develop Other Strategic Fuels – In 20 years, develop technologies to replace 50% (>15 billion gallons) of maritime fuel, off-road vehicle fuel, and rail fuel with low net GHG emission fuels.

Theme 2: Chemicals and Materials

Goal 2.1: Develop Low-Carbon-Intensity Chemicals and Materials – In 5 years, produce >20 commercially viable bioproducts with >70% reduced lifecycle GHG emissions over current production practices.

Goal 2.2: Spur a Circular Economy for Materials – In 20 years, demonstrate and deploy cost-effective and sustainable routes to convert bio-based feedstocks into recyclable-by-design polymers that can displace >90% of today's plastics and other commercial polymers at scale.

Theme 3: Climate-Focused Agricultural Systems and Plants

Goal 3.1: Develop Measurement Tools for Robust Feedstock Production Systems – In 5 years, develop new tools for measurement of carbon and nutrient fluxes in agricultural and bioeconomy feedstock systems that contribute to a national framework.

Goal 3.2: Engineer Better Feedstock Plants – In 5 years, engineer plants and manipulate plant microbiomes to produce drought tolerant feedstocks capable of growing on underutilized land with >20% improvement in nitrogen and phosphorus use efficiency.

Goal 3.3: Engineer Circular Food Protein Production Systems – In 5 years, demonstrate viable pathways to produce protein for food consumption including from biomass, waste, and CO_2 that achieve >50% lifecycle GHG emissions reduction and cost parity relative to current production methods.

Theme 4: Carbon Dioxide Removal

Goal 4.1: Develop Landscape-Scale Biotechnology Solutions – In 10 years, develop technologies to expand implementation of landscape-scale soil carbon sequestration and management techniques on tens of millions of acres, increasing soil health and drought resilience and supporting U.S. climate targets.

Goal 4.2: Enable Biomass with Carbon Removal and Storage (BiCRS) – In 9 years, demonstrate durable, scalable biomass CO_2 removal for <$100/net metric ton, on a path to enabling gigaton-scale removal.

Bold Goals Explored

Climate change is expected to produce radical changes to the environment, including extreme weather events, changing weather patterns, drifting ecological zones, and other rapid environmental changes that may outpace Nature's ability to adapt. Action is urgently needed to develop and implement less carbon-intensive processes for producing the fuels, chemicals, and materials that support society, and to implement practices that remove CO_2 from the atmosphere to ameliorate the long-term effects of climate change. In addition, these approaches for reducing GHG emissions and CO_2 removal should also minimize other harmful emissions, water use, habitat conversion, and other sustainability challenges. These efforts will require a comprehensive approach effectively integrating discovery research, use-inspired basic research, and applied research, development, demonstration, and deployment.

Given the cross-cutting nature of these all-of-government efforts, relevant goals for supporting climate change solutions are also described in the other sections of this report led by the U.S. Department of Agriculture (USDA), the Department of Commerce, and the National Science Foundation (NSF).

Theme 1: Transportation and Stationary Fuels

Context for the Bold Goals

Achieving overall net-zero GHG emissions in the United States requires major changes to shift the economy from fossil-based fuels to sustainable sources for the liquid fuels needed to power economic sectors that are traditionally difficult to power with sustainable approaches. The transportation sector currently represents 29% of gross U.S. emissions,[2] with the difficult-to-abate sectors of aviation, maritime, rail, and off-road transport contributing 26% of that total. As outlined in the multi-agency Transportation Decarbonization Blueprint,[3] as battery electric vehicles and clean hydrogen begin to reduce emissions from light-, medium-, and heavy-duty on-road vehicles, the share of emissions associated with these difficult-to-abate sectors is expected to rise. Solutions will likely still require sustainable liquid fuel production, with much of that relying on biomass and waste as feedstocks. In particular, recognition of the importance of biomass in decarbonizing aviation led to the Sustainable Aviation Grand Challenge which calls for producing more than 3 billion gallons of sustainable aviation fuels (SAF) by 2030, rising to 35 billion gallons in 2050.[4] Advances in harnessing biotechnology and biomanufacturing to produce transportation and stationary fuels will require ongoing and expanded R&D investments in three areas: expanding feedstock availability, producing SAF, and developing other strategic fuels.

Goal 1.1: Expand Feedstock Availability. There is great potential for expanding the use of renewable feedstocks in the United States due to a unique national strength in agriculture. The United States has an unparalleled ability to grow, harvest, store, and transport agricultural products on a massive scale. While this productivity is most evident for grain and oilseed crops, the potential exists to expand agricultural production of purpose-grown crops for bioenergy and bioproducts. Currently, roughly 368 million metric tons per year of biomass and biogenic wastes are available as feedstocks for conversion to a range of products, and estimates indicate this could be expanded to more than 1 billion tons.[5] There are, however, significant challenges to reliable and efficient biomass conversion to fuels and products stemming from the compositional variability of sources such as agricultural and forest residues, organic municipal waste streams, and dedicated herbaceous and woody crops. There are also opportunities to view CO_2 as a feedstock in combination with renewable energy and clean hydrogen. These feedstocks will be critical for

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[2] Inventory of U.S. Greenhouse Gas Emissions and Sinks: 1990-2021 | U.S. Environmental Protection Agency

[3] The U.S. National Blueprint for Transportation Decarbonization

[4] Sustainable Aviation Fuel Grand Challenge Roadmap | U.S. Departments of Energy, Transportation, and Agriculture with the U.S. Environmental Protection Agency

[5] 2016 Billion-Ton Report | U.S. Department of Energy

achieving transportation and fuels goals as well as providing sustainable feedstock for decarbonization efforts for chemicals and materials in **Theme 2**.

Goal 1.2: Produce SAF. Enhancements to increase sustainable feedstock production bring opportunities to pursue priority market needs like renewable replacements for aviation fuels. U.S. commercial aviation currently consumes approximately 10% of U.S. transportation energy and is projected to grow as a share of fuel demand. Air travel, which represents most emissions from aviation, will be difficult to electrify because batteries are not soon projected to achieve sufficient energy density to meet power and weight requirements for long-haul air travel. Conversion of plant biomass and waste feedstocks, including lignocellulosic biomass, municipal solid waste, and CO_2, to sustainable aviation fuel in combination with clean energy and hydrogen offers near-term potential to reduce aviation GHG emissions with minimal changes to current airport infrastructure due to the potential "drop-in" nature of the fuel. Biotechnology and complementary chemical catalysis approaches must be developed and deployed to maximize GHG emissions reduction for new SAF mixtures beyond the 50% reduction qualifying floor to be eligible for the tax credit established in the Inflation Reduction Act[6] and other policy frameworks. This includes the stretch goal of achieving at least 70% GHG reduction on more than half of the potential biomass and waste feedstocks outlined in Goal 1.1.

Goal 1.3: Develop Other Strategic Fuels. As light- and medium-duty vehicle liquid fuel use declines with adoption of battery-powered electric vehicles, biofuels should be integrated into new markets with limited medium- to long-term electrification potential. In addition to foreign demands, these markets include maritime, off-road, and rail transport and will likely continue requiring energy-dense liquid transportation fuels.[7] Stationary application fuels, like renewable natural gas, woody biomass, and low carbon-intensity fuels for process heat, will also play important roles in economy-wide decarbonization.[8]

R&D Needs

- Conduct research, development, and demonstration projects to reduce the carbon footprint of feedstock production, collection, transportation, and preprocessing. **(Goal 1.1)**
- Develop technologies capable of cost-effectively and sustainably pretreating heterogeneous waste streams and separating contaminants to increase the quantity and quality of available waste feedstocks. **(Goal 1.1)**
- Continue to address R&D barriers to SAF production as outlined in the roadmap developed jointly by DOE, USDA, and the Department of Transportation[9] by (1) conducting comparative, self-consistent analyses to understand how various technologies under development can work together to displace petroleum-derived jet fuel and (2) enabling the rapid progression from research and innovation to scale-up and commercial deployment. **(Goal 1.2)**
- Explore new routes to known intermediates in SAF production and produce new bio-based compounds that can be used for SAF with increased GHG emissions reductions. **(Goal 1.2)**
- Optimize bioconversion and processing of cellulosic feedstocks by developing production pathways capable of using a wide variety of feedstocks while establishing fuel quality standards and test methods. Such systems should consider local sourcing of feedstocks and smaller-scale processing options to enable distributed production systems closer to the point of use. **(Goal 1.3)**

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[6] Inflation Reduction Act of 2022 | U.S. Congress
[7] The U.S. National Blueprint for Transportation Decarbonization
[8] Industrial Heat Shot | U.S. Department of Energy
[9] Sustainable Aviation Fuel Grand Challenge Roadmap

Theme 2: Chemicals and Materials

Context for the Bold Goals

To achieve a net-zero emissions economy, significant changes are needed to the ways that chemicals, materials, and products are produced in the United States. Currently, thousands of everyday products ranging from plastics to lipstick and deodorant are manufactured from petroleum and natural gas.[10] Current production methods are also GHG emissions intensive, with the industrial sector accounting for 30% of gross U.S. GHG emissions.[11] The chemicals sector is the largest industrial GHG emitter with over 20% of industrial emissions, a significant portion of which may be eliminated using biomanufacturing and sustainable biomass resources. Chemicals, materials, and products can be derived from more sustainable, bio-based resources and produced in less carbon-intensive ways that promote broader reuse in a circular bioeconomy. To reduce GHG emissions in chemicals and materials production, ongoing and expanded R&D investments in harnessing biotechnology and biomanufacturing are needed in two areas: developing low-carbon-intensity chemicals and materials and spurring a circular economy for materials.

Goal 2.1: Develop Low-Carbon-Intensity Chemicals and Materials. Approximately 20% of every barrel of crude oil, and a significant fraction of natural gas, are used to make non-fuel products ranging from plastics to paints, solvents, and asphalt. Transitioning away from fossil resources requires renewable alternatives for all these products. Bio-based feedstocks and bioprocessing routes can reduce net GHG emissions, stabilize commodity chemical prices, and avoid supply chain disruptions. DOE has begun to address this need with the Industrial Heat Shot[12] which includes development of biomanufacturing processes that often operate near room temperature, requiring less process heat than incumbent petroleum-based processes.

Goal 2.2: Spur a Circular Economy for Materials. Currently, commodity polymer manufacturing (including plastics) is responsible for GHG emissions equivalent to the global aviation sector, and manufacturing these products is projected to represent >20% of annual global fossil fuels consumption by 2050.[13] Additionally, waste plastics accumulating in landfills and the broader environment is well recognized as a planetary-scale pollution crisis. Opportunities exist to produce biobased plastics to offset petroleum-derived plastic products, but use of biobased products must be expanded. Accordingly, an urgent global need exists to rapidly enable a more circular economy for today's fossil carbon-based polymers production and to source chemical building blocks for tomorrow's recyclable-by-design plastics from bio-based and waste sources. DOE is addressing this transition with its Strategy for Plastics Innovation,[14] a DOE-wide approach focused on GHG emissions reduction, new recycling technologies, sustainable manufacturing, and polymers redesign for improved end-of-life properties.

R&D Needs

- Use biotechnology to identify biological pathways and biochemical processes involved in the production of key molecules and increase the yield and process efficiency for chemicals produced from a range of carbon sources. **(Goal 2.1)**
- Develop innovations at the interface of biology and chemistry to produce platform chemicals and final products with greatest potential to reduce GHG emissions. **(Goal 2.1)**
- Conduct research to support regulatory efforts and safe commercialization of new products. **(Goal 2.1)**

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[10] Everyday Products and Uses Fact Sheet | Colorado Oil and Gas Association
[11] Industrial Decarbonization Roadmap | U.S. Department of Energy
[12] Industrial Heat Shot
[13] The New Plastics Economy: Rethinking the Future of Plastics | Ellen MacArthur Foundation
[14] Strategy for Plastics Innovation | U.S. Department of Energy

- Expand R&D for process development and scale-up to recycle and/or upcycle waste resources such as plastic waste, including through selective chemical and biological methods, with an emphasis on mixed and multi-component waste that is not recycled today. **(Goal 2.2)**
- Expand efforts to design or redesign materials such as plastics to improve end-of-life properties including increased recyclability and/or compostability where appropriate. **(Goal 2.2)**
- Establish pilot scale-up facilities to test new technologies from synthesis, manufacturing, and polymer processing to in-line application testing for materials and chemical synthesis and recycling. **(Goal 2.2)**

Theme 3: Climate-Focused Agricultural Systems and Plants

Context for the Bold Goals

Foundational to a net-zero GHG economy, changes to agriculture and production methods for plant-based resources will be needed to decrease the overall carbon intensity of feedstock production, a major source of CO_2 emissions. Emissions from the agricultural sector comprise 9% of the U.S. total, the majority of which are non-CO_2 emissions like nitrous oxide from soil and methane from enteric fermentation and manure management.[15] Developing practices that retain carbon in the soil or direct it toward plant growth are critical to transforming agriculture from a net GHG source to a net sink. These climate-focused goals are related to ongoing efforts and goals at USDA and DOE and will require R&D investments across government in three areas: developing measurement tools for robust feedstock production systems, engineering better feedstock plants, and engineering circular food protein production systems.

Goal 3.1: Develop Measurement Tools for Robust Feedstock Production Systems. Agricultural soil management practices contribute around 5% of total U.S. GHG source emissions and are a significant source of the world's total annual GHG production. In addition, nitrous oxide emissions from soil management practices accounted for approximately 74% of U.S. nitrous oxide emissions in 2021.[13] Furthermore, emissions from ammonia production account for around 1.8% of global CO_2 emissions, of which over 80% is used as fertilizer.[16] A focus on accurate quantification of these effects is needed to achieve the most efficient GHG reductions in the agricultural sector. In this area, USDA leads development of tools and data systems to measure, monitor, report, and verify carbon and nutrient fluxes for agricultural systems. These tools are important for developing climate-focused agricultural systems that reduce the carbon intensity of feedstock production and significantly add to the overall climate impact by shifting to a more sustainable bioeconomy.

Goal 3.2: Engineer Better Feedstock Plants. Advanced biotechnology is providing new ways to increase plant feedstock production and gain a much better understanding of processes that control carbon and nutrient flux in soils among microbes and plants. Continued R&D in these areas reflects the need to achieve parallel goals of increasing feedstock yield and resilience while lowering the overall carbon intensity of feedstock production and improving soil health and sustainability. Scientific understanding of plant biology is accelerating rapidly, especially as it relates to plant composition (e.g., plant cell wall), plant regulation (e.g., carbon partition and allocation), and improved sustainability in environmental, soil microbiome, and land-management contexts. Minimally domesticated bioenergy crops, like switchgrass, poplar, pine, and camelina, possess great potential for improvement due to broad natural variation. Existing crops like maize and sorghum have less variation due to decades of breeding but they have never been bred for both current usage yield (i.e., food) and for residue yield and composition.

Goal 3.3: Engineer Circular Food Protein Production Systems. This goal is focused on protein production-related research for climate solutions and complements a broader food production goal

[15] Inventory of U.S. Greenhouse Gas Emissions and Sinks | U.S. Environmental Protection Agency
[16] Ammonia: Zero-Carbon Fertiliser, Fuel, and Energy Store Policy Briefing | The Royal Society

described in the Food and Agriculture Societal Goal Report. Greater than 25% of global anthropogenic GHG emissions come from the global food system.[17] Currently, most non-aquatic food protein, whether from plants or animals, is produced through energy-intensive land use practices. In addition, protein production will need to be doubled by 2050 to feed the growing global population. To that end, new biotechnologies enabling food protein production from waste substrates through microbial bioprocesses could potentially increase production while reducing global agricultural land use. In turn, this would improve nutrient utilization efficiency, release agricultural land for carbon sequestration, and begin to restore global biodiversity. Microbially-produced protein is a decades-old concept with precedent in some marketplace niches. However, there is a shortage of work ongoing in the publicly funded research and development community related to microbial protein production from waste feedstocks. Advances in biotechnology and precision fermentation are setting the stage for revitalization of this sector.

R&D Needs

- Improve modeling and methods for estimating, measuring, and monitoring GHG sources and sinks and carbon cycling and sequestration in biomass and soils. **(Goal 3.1)**
- Develop a nationally applicable framework and associated tools for measuring and verifying carbon and nutrient flux in agricultural systems producing bioeconomy feedstocks. **(Goal 3.1)**
- Conduct R&D on plants (including algae) and soil microbial communities to generate knowledge for producing new dedicated feedstocks using less carbon-intensive practices. **(Goal 3.2)**
- Develop approaches to measure overall improvements in engineered plants against established baselines based on current production crops and varieties. **(Goal 3.2)**
- Develop bioprocessing approaches that enable scale-up of biotechnology-based protein production while maintaining or improving quality, and thoughtfully matching large-scale waste feedstocks to efforts in synthetic biology and bioprocess engineering. **(Goal 3.3)**
- Develop rigorous and transparent process analyses relative to existing food protein production pathways to inform development of sustainable bioprocesses. **(Goal 3.3)**
- Conduct research to inform regulatory efforts and safe commercialization of new products. **(Goals 3.2 and 3.3)**

Theme 4: Carbon Dioxide Removal

Context for the Bold Goals

Reducing GHG emissions alone is not enough for the U.S. to reach net zero emissions by 2050 and keep a 1.5°C limit on global temperature rise within reach.[18] Effective approaches for CO_2 removal from the atmosphere and durable sequestration are also needed to achieve net negative emissions on a massive scale. The Intergovernmental Panel on Climate Change (IPCC) estimates that >10 gigatons of CO_2 per year net negative global emissions will be required by 2100.[19] Biotechnology can play a large role in CO_2 removal through a variety of potential pathways. These advances in harnessing biotechnology and biomanufacturing for CO_2 removal will require ongoing and expanded R&D investments in two areas: developing landscape-scale biotechnology solutions and enabling biomass with carbon removal and storage.

Goal 4.1: Develop Landscape-Scale Biotechnology Solutions. Most bio-based carbon in terrestrial systems is stored underground in the soil system. It has been demonstrated that crops, such as perennials, and landscape management practices, such as no-till agriculture, can steadily increase soil health and soil

[17] Food Systems Are Responsible for a Third of Global Anthropogenic GHG Emissions | Crippa, M., et al. 2021. *Nature Food*
[18] Negative Emissions Technologies and Reliable Sequestration | National Academies of Sciences, Engineering, and Medicine
[19] Climate Change 2014: Mitigation of Climate Change. Contribution of Working Group III to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change | IPCC

organic carbon (SOC) from year to year.[20] Biotechnology can further enhance these approaches through improved plant feedstock and root microbiome design (see Goal 3.2). Additional benefits to improved SOC, such as increased water retention and plant yields, suggest that these techniques can improve overall agricultural system effectiveness while dramatically enhancing the system's ability to sequester carbon. These changes to improve SOC, along with better land management and deploying more plants in areas not already slated for biomass feedstock or crop growth, provide landscape-scale solutions that can be coupled with long-term, durable preservation approaches.

Goal 4.2: Enable Biomass with Carbon Removal and Storage (BiCRS). In addition to sequestering carbon in soils (Goal 4.1), a variety of BiCRS approaches are needed to effect long-term, durable CO_2 removal. These approaches can utilize biomass from a variety of purpose-grown crops or wastes and durably store biomass carbon in long-lived solid carbon materials or in appropriate geological formations. Enabling CO_2 capture from the atmosphere and storage at gigaton scales for <$100 per net metric ton is a core goal of DOE's Carbon Negative Shot.[21]

R&D Needs

- Develop genetic engineering and technology tools for high yield crops and forest trees with deeper and more recalcitrant root systems to increase SOC. **(Goal 4.1)**
- Address knowledge gaps related to plant-soil interactions that promote SOC accumulation without reducing nutrient mineralization and develop a predictive ecological landscape conceptual framework for understanding soil organic matter dynamics. **(Goal 4.1)**
- Determine the most cost-effective BiCRS pathways and how it can complement other biomass uses as part of a complete carbon management strategy. **(Goal 4.2)**
- Determine the best long-lived solid carbon materials produced through biological systems and explore increasing capture of atmospheric CO_2 into materials using biomimetic or cell-free systems, bioelectric approaches, and bioinorganic materials. **(Goal 4.2)**

Stakeholder Consultation

The bold goals and associated R&D needs summarized in this report build upon recent reports and assessments related to climate change and energy solutions developed over the last several years through workshops and with input from stakeholders across government and the private sector, as well as input from subject matter experts at DOE national laboratories. Additionally, an industry listening session on climate change solutions was hosted by the White House in November 2022, and public input was collected through an Office of Science and Technology Policy-led Request for Information posted in December 2022.[22] Input from this outreach informed the bold goals, R&D needs, and other sections of this report. Additional stakeholder input included white papers, briefings, reports, and publications.

Enhancing Biosafety and Biosecurity

Effective biosafety and biosecurity throughout biotechnology development and the biomanufacturing lifecycle are critical for maintaining a strong and resilient bioeconomy. In the area of climate change and energy solutions, biosafety and biosecurity may be viewed through the lens of three categories for the purposes of pinpointing vulnerabilities: (1) process input or feedstock production, (2) manufacturing and supply, and (3) end-use and final product fate. Biosafety practices and controls reduce the risk of unintentional exposure or release of pathogens, toxins, and harmful biological materials. Biosecurity measures mitigate the risk of loss, theft, misuse, diversion, or intentional release of pathogens, toxins, and

[20] Novel Technologies for Emission Reduction Complement Conservation Agriculture to Achieve Negative Emissions from Row-Crop Production | Northrup, D. L., et al. 2021. *PNAS*
[21] Carbon Negative Shot | U.S. Department of Energy
[22] Request for Information; National Biotechnology and Biomanufacturing Initiative | Office of Science and Technology Policy

biological materials or research-related information and technology, as well as the introduction of harmful materials into the biotechnology and biomanufacturing ecosystem.

Existing Biosafety and Biosecurity Measures

There are ongoing and planned activities to enhance biosafety and biosecurity for biotechnology and biomanufacturing in several critical areas, including research, workforce development, and culture change, as will be addressed in the Biotechnology and Biomanufacturing Innovation Initiative (BBII) in Section 9 of Executive Order 14081. Many of these activities apply across societal goals. There are also ongoing and planned research efforts specifically relevant to biosafety and biosecurity innovation for climate and energy solutions. For example, DOE's Secure Biosystems Design program focuses on building upon advances in genome science and synthetic biology to design and engineer DOE-relevant biological systems with built-in biocontainment measures. The Biosecurity for Bioenergy Crops pilot study under DOE's Biopreparedness Research Virtual Environment (BRaVE) effort is developing understanding of threats to bioenergy crops as part of a larger agnostic approach to addressing potential biothreats, along with related mitigation strategies. In addition, ongoing research efforts not focused solely on biosafety and biosecurity include integrated tasks and activities related to biosafety and biosecurity innovation for a range of applications (e.g., Advanced Biofuels and Bioproducts Process Development Unit, ecosystem testbed platforms, and algae test bed facilities at DOE national laboratories). The National Nuclear Security Administration at DOE is also initiating a Bioassurance program to advance U.S. capabilities to anticipate, assess, detect, and mitigate biotechnology and biomanufacturing risks and integrate biosecurity into biotechnology development.

Recommended New Biosafety and Biosecurity Measures

Moving forward, it is critical to continue efforts and bolster recommended activities covered in BBII, ranging from training to research to public-private partnerships. Specifically in R&D related to biosafety and biosecurity innovation during the development of climate change solutions, it is important to consider the molecular processes, system components, and integrated system (i.e., spanning process input or feedstocks, manufacturing, supplies, products, and product fate) along with the pace of innovation in biotechnology and biomanufacturing that includes technology integration.

Opportunities for Public-Private Collaboration

Existing Public-Private Partnerships

Existing public-private partnerships related to the bold goals primarily fall into the categories of databases, user facilities, and joint funding opportunity projects. DOE encourages funded collaborations between national laboratories and private companies to enable industry to benefit from public sector expertise and vice versa. Open access, online basic science analysis platforms such as the DOE Systems Biology Knowledgebase and the National Microbiome Data Collaborative and user facilities such as the DOE Joint Genome Institute and Environmental Molecular Science Laboratory, which collect DNA sequence and omics information, enable efficient use of new microorganisms and plants for a variety of purposes, including production of fuels and products. Databases with information about land use, feedstocks, and climate enable appropriate location siting and supply chain planning. Other user facilities such as the Advanced Biofuels and Bioproducts Process Development Unit (ABPDU) and the Biomass Feedstock National User Facility (BFNUF) enable companies to de-risk conversion technologies, feedstock supply, and preprocessing technologies. BFNUF has worked with over 40 industry customers across the bioenergy supply chain to address feedstock-related challenges in preprocessing and scale-up of the bioeconomy. ABPDU, housed at Lawrence Berkeley National Laboratory since 2009, is a scale-up facility with cutting-edge equipment and a dedicated team of experts. ABPDU has helped over 75 companies develop prototypes and scale technologies. Companies that prototyped at ABPDU have raised over $2 billion in private funding and transitioned 17 products to market.

Opportunities for U.S. Government Incentivization of Private Sector

Compelling opportunities exist for the U.S. government to build additional databases, develop standards, increase R&D funding opportunities, and expand user facilities for scale-up. Investments in workforce development and direct incentives, as well as private industry participation and feedback, are critical to the success of the goals outlined in this report.

Collecting information and making it available in databases should be prioritized to support the private sector, underpinned by the Data Initiative described in Section 4(a) of Executive Order 14081. All varieties of omics data, in addition to phenotype and imaging data, should be made publicly accessible in a Findable, Accessible, Interoperable, and Reusable (FAIR) manner whenever possible, while providing appropriate data security to protect personal identifiable and sensitive information. In addition, applied R&D process data, such as life-cycle assessments, technoeconomic analyses, and standards, should be made broadly available to help industry use best practices to understand, demonstrate, and improve their sustainability impacts and attract investment.

The private sector can play a key role in populating these databases. For example, through public-private partnerships, a labeling and quantification system could be developed for consumers to make informed choices about the products they purchase. Quality standards for different feedstocks and bio-based products should be developed to support robust supply chain development and market entry, and standards for new industrial microbes and plants would also aid adoption. The private sector, along with government agencies like National Institute of Standards and Technology, USDA, DOE, NSF, and others, should play an integral role in developing these standards and validating the test methods.

New public-private partnerships and research consortia with shared precompetitive goals for commodity fuel and chemical production that benefit climate outcomes can help address key industry challenges preventing market entry and expansion. The DOE Agile Biofoundry and the Department of Defense BioMADE are successful examples of this type of consortium. Expanding similar efforts would help propel the bioeconomy. Ongoing private sector input on the most critical research challenges would help direct these efforts and enable industry growth. Interdisciplinary and international collaborations should be greatly expanded to leverage expertise across fields and spur innovation globally.

New and expanded user facilities and incentives for the private sector to develop scale-up capacity are needed to de-risk new technologies. Field trials for new plant feedstocks and shared, common gardens for experimentation, phenotyping, and validation should be established to enable new feedstocks and develop feedstock standards. Expanded shared, fit-for-purpose fermentation and downstream processing scale-up facilities with state-of-the-art process monitoring and control capabilities are needed to help companies develop process understanding and control strategies for production scale. A network of these facilities is also needed so companies can create batches large enough for product testing to confirm performance and attract investors and customers. The current network of facilities in the United States does not meet demand and lags overseas networks, driving some companies to conduct scale-up efforts abroad.

A trained workforce is critical to carry out the efforts described in this report. The U.S. government can support this through expanded STEM workforce development programs and other activities that support implementation of Section 7 of Executive Order 14081 on promoting bioeconomy workforce development. In addition, while the incentives created by the Inflation Reduction Act provide a good foundation, they may not be sufficient to overcome the capital risks faced by developers or to fully incentivize farmers to produce sustainable biomass, absent further policy support. For example, incentives for production of low-carbon-intensity feedstocks and products produced and manufactured in the United States would help overcome the high capital risk of needed advancements, along with creating or expanding incentives that encourage companies to use raw materials and products with lower carbon intensity. Furthermore, incentives could support farmers to produce sustainable biomass; these could include tax incentives and subsidies for inputs, equipment, and facilities that lead to lower carbon intensity feedstock production.

Opportunities for Public Participation

Public participation and input will be essential as R&D programs are developed and implemented to harness biotechnology and biomanufacturing to achieve the climate solution goals outlined in this report. For example, opportunities for public participation may include R&D funding opportunities related to the specific goals in this report, as well as input at workshops, sessions at meetings, listening sessions, and requests for information. Furthermore, public trust, public education, and public acceptance are critical for widespread adoption of biotechnologies. Therefore, the public must be engaged at many points throughout the technology development process. Full transparency and strong national regulatory oversight, including technology-specific risk assessments, are critical to ensuring public trust, understanding, and acceptance.

Biotechnology and Biomanufacturing R&D to Further Food and Agriculture Innovation

In collaboration with other U.S. Federal Government departments and agencies, this report was authored by the U.S. Department of Agriculture

Executive Summary

Biotechnology and biomanufacturing are providing transformative solutions to many of the greatest challenges facing U.S. agriculture and food production, including climate change, food and nutrition insecurity, and pests and diseases in agricultural plants and animals. Naturally occurring genetic variation offers tremendous promise for improvements in agricultural plants, animals, and microorganisms, particularly when paired with accelerated breeding strategies and biotechnology, including genome editing. Biotechnology and biomanufacturing can provide needed value-added income streams to America's farmers, ranchers, producers, and forest landowners in the bioeconomy.

Applying biomanufacturing and biotechnology in food and agriculture requires strategic and sustained investment in technology platforms. Such investment can shorten the time to commercialization and reduce risk for new product development, so innovators can successfully manage the costs of innovation prior to marketing and revenue generation. Investment and support are also needed to expand the availability and deployment of currently available solutions. Additional needs include support to research and build marketplace demand, expand the workforce, ensure abundant feedstock supplies, build or repurpose physical infrastructure, and develop other partnerships and processes necessary to grow the bioeconomy.

The U.S. Department of Agriculture (USDA) has a critical role in advancing the bioeconomy by providing leadership and scientific research to enable American farmers and foresters to remain globally competitive and to enable American businesses to produce innovative products. USDA has outlined an ambitious vision for bioeconomy research and development (R&D) that fits into three themes: (1) improving sustainability and resource conservation while increasing agricultural productivity; (2) improving food nutrition, quality, and consumer choice; and (3) protecting plants and animals against environmental stressors.

In **Theme 1**, we describe goals for increasing agricultural productivity, increasing climate-smart feedstock production and biofuel usage, reducing nitrogen and methane emissions, and reducing food waste. The future of U.S. agriculture depends on improvements in production capacity, efficiency, and environmental stewardship. To spur economic growth and meet the demands of a growing global population, agricultural lands need to be more productive and use both inputs and outputs efficiently.

In **Theme 2**, we describe goals for developing new food and feed sources, enhancing nutrient density in foods, and reducing foodborne illness. Innovations in food and feed can boost both dairy and cultivated protein companies, for example, sustainably expanding the range of available protein options. Improving nutritional quality and reducing foodborne illness are essential for increasing food security.

In **Theme 3**, we describe goals for detecting and mitigating pests and pathogens as well as improving resilience to biotic and abiotic stress. Climate change is contributing to increased incidences of pest and disease outbreaks. Unprecedented droughts and floods, unseasonably warm winters, late frosts, and wet springs are changing farmers' needs and how they manage agricultural production.

Achieving these bold goals will require actions from the private sector, public-private partnerships, and effective coordination with domestic and international partners. The United States has long been a global leader in agricultural research and development to improve productivity and promote more efficient use of natural resources in agriculture. By leveraging innovation in biotechnology and biomanufacturing, we can expand the toolbox for farmers, ranchers, and other producers to meet the many challenges in food and agriculture.

Bold Goals for Harnessing Biotechnology and Biomanufacturing

The following goals are transformative solutions for food and agriculture intended to provide a broad vision for the U.S. bioeconomy. These should not be read as commitments by USDA to undertake specific activities. Achieving these bold goals will require significant prioritization of R&D investments and efforts across the U.S. government, as well as actions from the private sector, and state, local, and tribal governments.

Theme 1: Improving Sustainability and Resource Conservation While Increasing Agricultural Productivity

Goal 1.1 Increase Agricultural Productivity – Over the next 10 years, increase agricultural total factor productivity growth to meet global food and nutrition security needs while improving natural resource use efficiency and conservation, toward the global goal of increasing agricultural productivity by 28% in the next decade.[23]

Goal 1.2: Increase Climate-Smart Feedstock Production and Biofuel Usage – By 2030, increase climate-smart production of conventional and alternative agricultural and forestry feedstocks for biomanufacturing, biobased products, and biofuels; reduce the lifecycle greenhouse gas intensity of biofuels by 50%; and expand overall biofuel blend rates in U.S. liquid transportation fuels by 50%.

Goal 1.3: Reduce Nitrogen Emissions – Within the next 5 years, develop technologies to reduce nitrogen emissions from agriculture, including by decreasing the need for applied nitrogen by increasing nitrogen use efficiency in plants and improving fertilizer products and practices.

Goal 1.4: Reduce Methane Emissions – By 2030, reduce methane emissions from agriculture, including by increasing biogas capture and utilization from manure management systems, reducing methane from ruminant livestock, and reducing methane emissions from food waste in landfills, to support the U.S. goal of reducing greenhouse gas emissions by 50%[24] and the global goal of reducing methane emissions by 30%[25].

Goal 1.5: Reduce Food Loss and Waste – By 2030, reduce food loss and waste by 50%[26], including by developing and commercializing new technologies and encouraging adoption of new and existing technologies.

Theme 2: Improving Food Nutrition, Quality, and Consumer Choice

Goal 2.1: Develop New Food and Feed Sources – Develop new food and feed sources, including production of novel or enhanced protein and fat sources at scale, to support the United Nations Sustainable Development Goal to eliminate global hunger by 2030[27].

Goal 2.2: Enhance Nutrient Density in Foods – Within the next 20 years, enhance nutrient density in agricultural plants and animals, develop underutilized plants and animals that have enhanced nutrient density, and build on traditional ecological knowledge to better utilize and conserve culturally important and nutritionally relevant plants and animals.

Goal 2.3: Reduce Foodborne Illness – Reduce incidence of foodborne illness, including with new and improved screening tools, toward meeting goals set in Healthy People 2030,[28] such as a 25% reduction in *Salmonella* illnesses.

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[23] OECD-FAO Agricultural Outlook 2022-2031 | Organisation for Economic Co-operation and Development and the United Nations Food and Agriculture Organization
[24] Fact Sheet: President Biden Sets 2030 Greenhouse Gas Pollution Reduction Target | White House
[25] U.S. Methane Emissions Reduction Action Plan | White House
[26] Food Waste FAQs | U.S. Department of Agriculture
[27] U.N. Sustainable Development Goals: Goal 2 – Zero Hunger | United Nations
[28] Foodborne Illness | U.S. Department of Health and Human Services

Theme 3: Protecting Plants and Animals Against Environmental Stressors
Goal 3.1: Increase Capacity to Detect and Mitigate Pests and Pathogens – Within the next 5 years, improve capacity to detect and mitigate high-consequence existing and emerging animal and plant pathogens and pests, especially disease-vectoring and damaging pests.
Goal 3.2: Improve Resilience to Biotic and Abiotic Stress – Within the next 20 years, increase resilience of agriculture and forestry and develop tools that increase resilience to biotic stress (disease and pest threats) and abiotic stresses (including extremes in drought, heat, cold, and precipitation).

Bold Goals Explored

Theme 1: Improving Sustainability and Resource Conservation While Increasing Agricultural Productivity

Context for the Bold Goals

Innovations in agriculture—including plant and animal breeding, agricultural inputs, and equipment—have enabled continuing growth in agricultural output. These innovations can help tackle multiple challenges at once, allowing producers to conserve resources and improve environmental outcomes while meeting the world's food, fiber, and renewable needs. Biotechnology and biomanufacturing present major opportunities to improve sustainability and resource conservation and to increase yields while decreasing inputs and related costs. An estimated 30 to 40% of food is wasted in the United States; reducing food loss and waste can improve food security, reduce agricultural inputs, and reduce greenhouse gas emissions[29]. In addition, expanding markets for bioenergy and biobased products can help achieve greenhouse gas mitigation goals. Supporting the bioeconomy and reducing costs and barriers to entry can bring new economic growth opportunities across the United States, including rural areas where feedstocks are grown and urban areas where tree maintenance provides residual biomass. Forest thinning in areas between homes and forests can provide additional feedstocks while helping to reduce wildfire risk and protect vulnerable habitats and communities.

R&D Needs

To support increases in agricultural productivity **(Goal 1.1)**:

- Better understand genetic, physiological, environmental, and biochemical constraints on yield to develop plants and livestock with higher production potential.
- Use accelerated breeding strategies and biotechnology to improve plants, animals, and microorganisms to enhance productivity and reduce environmental impacts of agriculture.
- Bolster research in innovative approaches and technologies—including precision agriculture and circular and nature-based solutions—that improve sustainability; reduce inputs; and rebuild soil health, carbon, and organic matter.

To support climate-smart feedstock production and biofuel usage **(Goal 1.2)**:

- Accelerate research into climate-smart feedstocks with reduced carbon intensity, learning from relevant Partnerships for Climate-Smart Commodities projects, including emerging feedstocks such as hemp and camelina, and feedstocks that are derived from agricultural waste, tree removal and wildfire fuel reductions, and coproducts to support the circular economy.

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[29] Food Waste FAQs | U.S. Department of Agriculture

- Develop tools that rapidly assess and track feedstock qualities to evolve markets that reward producers for product quality in addition to yield.
- Develop biochemical and biomanufacturing processes, including enzymatic and microbial processes, for efficiently converting feedstocks into intermediates and products at scale.
- Develop technologies to economically move, store, and process biomass prior to its use as feedstocks for biomanufacturing or conversion into biobased products.
- Expand upon biorefinery technologies to efficiently break down biomass into its components (e.g., lignin, hemicellulose, and cellulose); to convert lignin and hemicellulose into plastics, adhesives, and low-energy building materials; and to convert cellulose fiber into nanomaterials and cellulose derivatives for fibers, coatings, renewable packaging, and other products.

To support reduction of nitrogen emissions **(Goal 1.3)**:

- Continue research into efficient nutrient management practices, such as precision application, more efficient delivery systems, and sustainable fertilizer formulations that enable more efficient nutrient cycling with reduced environmental impact.
- Improve methods to reclaim nitrogen in wastewater by growing crops such as algae and duckweed for fertilizer and feedstocks for the bioeconomy.
- Bolster research into biostimulants that increase nitrogen use efficiency and replenish nitrogen stores in soil as part of an integrated approach to reducing fertilizer use, such as genome-edited soil microorganisms to enhance biological nitrogen fixation.
- Use accelerated breeding strategies and biotechnology to develop plants with reduced reliance on inputs and that increase uptake, storage, and recycling of soil nitrogen and phosphorus.
- Characterize materials that improve soil nitrogen balance and soil health, particularly materials that may be considered waste, such as biochar.

To support reduction of methane emissions **(Goal 1.4)**:

- Develop new and improve existing tools and models to accurately assess methane fluxes from agricultural systems.
- Develop affordable and efficient tools to capture biogas from manure management systems; use methane for power generation and other purposes.
- Bolster research into feed sources, new feed additives, and feed ingredients that reduce enteric methane emissions from ruminants and from aquaculture.
- Develop new technologies and innovative production systems that do not require rice production in paddies that generate methane-producing anaerobic bacteria.

To support reduction of food loss and waste **(Goal 1.5)**:

- Use accelerated breeding strategies and biotechnology to develop plants with traits that extend shelf life, such as reduced browning from bruising or resistance to mold growth.
- Improve or develop strategies to measure food waste, including both edible food and non-edible waste such as banana peels, bones, and eggshells, anywhere along the food chain.
- Bolster research into methods, products, and tools that prevent or reduce food loss from spoilage, pests, mold, and inadequate climate control, including sustainable, user-friendly, and biodegradable packaging and biobased coatings that extend product freshness and shelf life.
- Develop and expand strategies to increase food recovery or recycling programs at scale, including advanced biochemical and microbial systems for efficient conversion of food waste into feed, fertilizers, materials, bioproducts, and fuels.

Theme 2: Improving Food Nutrition, Quality, and Consumer Choice

Context for the Bold Goals

The United Nations Food and Agriculture Organization (FAO) estimates that by 2050 we will need to produce 60% more food to feed a world population of 9.3 billion[30]. Food must be nutritious as well as abundant. In the United States, poor nutrition is a leading cause of illness, associated with 600,000 deaths per year and linked with increased risk of obesity, diabetes, and heart disease as well as broader impacts including higher healthcare costs and decreased productivity[31]. Foodborne illness causes an estimated 48 million illnesses and 3,000 deaths each year in the United States[32]. In addition to increasing productivity, biotechnology and biomanufacturing can spur development of novel food sources with improved sustainability, including new crops and protein sources, which can augment our current food system and help provide equitable access to nutritious foods. Such innovation can also equip farmers and food manufacturers to reduce foodborne illness and meet changing consumer demand. Traditional ecological knowledge is an essential and powerful resource for improving nutrition. Many native plants and animals play vital roles in the cultures and economies of the people of the United States, particularly Indigenous communities with long-standing connections to native forests and grasslands.

R&D Needs

To support development of new food and feed sources **(Goal 2.1)**:

- Expand research into food components that make novel foods more palatable, affordable, easier to prepare, and more easily incorporated into manufactured foods.
- Research the structural design and food architecture of alternative protein (e.g., plant-based, fermentation-derived, and cell-cultured) products, including how plant and microbial materials compare to animal-based products.
- Identify and conduct feasibility studies for high-volume, low-cost protein and fat sources that could be used in food or feed, including products resulting from precision fermentation and co-products or waste streams from other industries.
- Develop and validate science- and risk-based processes for crop segregation, grain management and processing, and other controls to safely enable production of animal proteins in crops while mitigating potential commingling and allergen cross-contact in food supply chains.
- Bolster research into animal diets with improved digestibility and enhanced amino acid profiles, including integration of amino acids in animal diets, that improve conversion of feeds into food.
- Bolster research into alternative feed ingredients for livestock and aquaculture, including plants, algae, or seaweeds, that can enhance or replace feed ingredients.

To support enhancement of nutrient density in foods **(Goal 2.2)**:

- Use accelerated breeding strategies and biotechnology to develop plants and animals with enhanced nutrient density, including enhanced levels of micronutrients and nutraceuticals.
- Expand the range of organisms that can be used for nutritional purposes and enhance the nutrient density of plant and animal species that are currently used in agriculture.
- Expand joint research with tribes and other guardians of traditional ecological knowledge regarding cultivation of culturally important foods.
- Identify niche markets and opportunities for expanding production of culturally important nontimber forest products and wetland and grassland food species.

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[30] Feeding the World Sustainably | United Nations
[31] Food and Nutrition Security | U.S. Department of Agriculture
[32] Foodborne Illness and Disease | U.S. Department of Agriculture

To support reduction of foodborne illness **(Goal 2.3)**:

- Use accelerated breeding strategies and biotechnology to develop plants and animals that are less likely to carry pathogens that cause food-related infections.
- Develop risk-based tools to identify virulence factors and antimicrobial resistance in pathogens.
- Research methods to reduce occurrence of and mitigate pathogens that cause food-borne illness in food systems, including in both production settings and processing facilities.
- Develop rapid screening, detection, and quantification technologies and a national network for pathogens, chemical contaminants, and physical hazards.

Theme 3: Protecting Plants and Animals Against Environmental Stressors

Context for the Bold Goals

U.S. agricultural production is under increasing pressure from biotic and abiotic stressors. Climate change is driving more frequent and severe weather events, such as unprecedented droughts in California and floods in the Mississippi River basin. The changing climate is also contributing to pest and disease outbreaks as increased travel and trade lead to additional pest and pathogen invasions. These effects compound: pests and disease may have greater impacts on weather-stressed plants and animals. Globally, up to 40% of crop production is lost to pests, with costs to the global economy estimated at over $70 billion for invasive insects and $220 billion for plant diseases annually[33], with additional losses due to abiotic stresses like drought and floods. Each year, an estimated $300 billion is lost to animal diseases in livestock, globally[34]. In the United States, for example, from December 2022 through March 2023, over 58 million chickens, turkeys, ducks, and other poultry were affected by highly pathogenic avian influenza[35]. Livestock losses due to heat stress are expected to increase with climate change, reaching $40 billion annually by the end of the century[36]. Innovation in biotechnology and biomanufacturing can improve resiliency of crops and livestock, protect yields, improve animal health, and reduce emergence of zoonotic disease.

R&D Needs

To support capacity to detect and mitigate pests and pathogens **(Goal 3.1)**:

- Develop and validate rapid screening, detection, and quantification methods for pathogens, with accessible, timely, and accurate laboratory services nationwide.
- Develop commercially viable countermeasures for high-consequence diseases in plants and animals, including animal vaccines and antivirals.
- Begin research into molecular technologies to induce plant and animal defense responses, including plants that can detect, report, signal, and self-treat infection.
- Expand research on integrated pest management of pathogen-carrying pests, such as biocontrol agents, sterility, gene drives, pheromones, biorationals, and plant-incorporated protectants.
- Use genome sequencing to characterize new plant and animal pathogen isolates and identify their potential to acquire novel host ranges, including the potential to become a zoonosis.

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[33] Climate Change Fans Spread of Pests and Threatens Plants and Crops, New FAO Study | United Nations Food and Agriculture Organization

[34] Animal Health Through an Economic Lens | World Organisation for Animal Health

[35] 2022–2023 Confirmations of Highly Pathogenic Avian Influenza in Commercial and Backyard Flocks | U.S. Department of Agriculture

[36] Heat Stress for Cattle May Cost Billions by Century's End | Cornell Chronicle

- Expand screening for and sequence the genomes of agricultural plants and animals and their wild relatives that are resistant to pests and disease; use accelerated breeding strategies and biotechnology to develop plants and animals with improved disease resistance.

To support resilience to biotic and abiotic stress **(Goal 3.2)**:

- Use accelerated breeding strategies and biotechnology to develop plants and animals, including beneficial insects, that are adapted to present and predicted climates, with increased production under abiotic stress.
- Improve resistance screening and use accelerated breeding strategies and biotechnology in native tree species to improve resistance to pests and pathogens; develop assisted migration protocols to find, breed, and promote resilient trees.
- Increase understanding of agricultural and forest ecosystem dynamics in the face of stressors across scales to enhance resiliency and improve landscape health.

Overarching R&D Needs

To support biotechnology and biomanufacturing innovation throughout food and agricultural systems, USDA has identified four overarching R&D needs: (1) scale-up, standardization, and regulatory science; (2) plant, animal, and microorganism genome to phenome; (3) data analytics, infrastructure, and sharing; and (4) affordability, equitable access, and consumer perception. Partnerships across all sectors will be key to success in all of these R&D needs, especially in scaling the bioeconomy.

Scale-Up, Standardization, and Regulatory Science

- Build sufficient shared pilot facilities and intermediate-scale infrastructure that could be used by multiple organizations, reducing the time and cost to scale-up new technologies and products.
- Develop an ecosystem of biomanufacturing facilities (including for precision fermentation) close to feedstocks and workforce development opportunities; co-locate and coordinate food and fuel production facilities and processes so that co-products and waste can support circular economies.
- Develop new public research infrastructure and a matching skilled workforce to support the scale-up of biomanufacturing processes.
- Train the next-generation biomanufacturing workforce at pilot facilities, including operators for fermentation processes, who do not require formal education but do need specialized training.
- Develop standardized biomanufacturing methods, tools, and equipment.
- Develop standardized systems for measuring nutritional characteristics of different ingredients as well as sensory properties such as olfactory components, mouthfeel, taste, and texture.
- Develop standardized methods for measuring sustainability and conducting related assessments such as lifecycle analyses (LCAs).
- For all areas of innovation, increase investments in regulatory science to support regulatory review and safe commercialization of new products, such as through the USDA Biotechnology Risk Assessment Research Grants (BRAG) Program[37].

Plant, Animal, and Microorganism Genome to Phenome

- Support public plant and animal breeding infrastructure to identify beneficial genes, pathways, and regulatory controls that perform in varying production environments.
- Increase capacity to screen species for relevant agricultural traits and enable data collection with advanced imagery, spectra, and sensors to better describe phenotypes.

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[37] Biotechnology Risk Assessment Research Grants (BRAG) Program | U.S. Department of Agriculture

- Improve access to sequencing, bioinformatics, genomics-based breeding, genome editing, and other innovative techniques for improving diverse plants, animals, and microorganisms; identify and alleviate bottlenecks in crop transformation and regeneration methods.
- Sequence and annotate genomes of agriculturally relevant plants, animals, and microorganisms, including domesticated plants and animals and their wild relatives, pest and beneficial arthropods, weeds, plant and animal pathogens, and key ecosystem microbiomes.
- Expand, curate, phenotype, and sequence germplasm and genetic resource collections, including the USDA National Plant Germplasm System, Animal Germplasm Collection, and U.S. National Culture Collection.

Data Analytics, Infrastructure, and Sharing

- Forge partnerships to improve data collection, analytics, infrastructure, and sharing, including improvement of syntactic and semantic data and leverage Findability, Accessibility, Interoperability, and Reusability (FAIR) principles, while respecting intellectual property rights.
- Develop customizable digital twins to mimic major agriculture, forestry, or food systems, including plants, animals, and microorganisms.
- Integrate digital tools into agriculture and forestry operations by promoting precision agriculture, screening, and sensing technologies that support site-specific management systems.
- Use artificial intelligence (AI) and machine learning to enhance diagnostic applications, genome sequence analysis, and functional genomic annotation.
- Combine AI and autonomous robotic systems in programmable, large-scale, data-driven farming and forestry practices.
- Develop tools to better forecast production of resources from agriculture and forestry.
- Develop an open-access "Food Data Web" integrating production, consumer, environmental, and health data related to food.

Affordability, Equitable Access, and Consumer Perception

- Expand research into consumer perception, preference, acceptance, and adoption of alternative packaging, biobased products, biofuels, and foods developed with biotechnology and biomanufacturing.
- Understand how labeling for production practices (e.g., climate-smart, organic), sustainability (e.g., water usage, carbon footprint, biodiversity), food safety, nutritional content, and other attributes influence consumer behavior and purchasing of products and how effects vary across settings (e.g., restaurants, online, on-site grocery).
- Research the efficacy of education and engagement methods for informing consumers about innovative products to inform methods to increase awareness and expand the demand.

Stakeholder Consultation

In November 2022, the White House convened a roundtable on food and agriculture, in which USDA's Chief Scientist and other USDA staff heard from stakeholders about sustainability, nutrient density in foods, data sharing, standardization of methods, consumer acceptance, regulatory and trade concerns, biomanufacturing infrastructure, bioeconomy workforce, and other topics. The White House Office of Science and Technology Policy published a Request for Information and held a virtual public listening session on January 9, 2023; many commenters were from the agricultural sector. Additional R&D-focused listening sessions were hosted by the Good Food Institute and by land grant institutions at Iowa State University; regulation-focused listening sessions were hosted by the American Seed Trade Association, Biological Products Industry Association, and Biotechnology Industry Organization.

All stakeholders discussed the need for biomanufacturing scale-up infrastructure and a trained workforce to fill jobs across the bioeconomy. Many stakeholders described having to go outside of the United States to find fermentation capacity. Facilities and processes are needed within the United States for scaling up proof-of-concept or small-scale biomanufacturing to commercial scale. Stakeholders also described the need for risk-proportionate regulation of biotechnology, international alignment of regulation, and communication across the value chain about innovations in food and agriculture.

Enhancing Biosafety and Biosecurity

Existing Biosafety and Biosecurity Measures

USDA has many efforts to advance biosafety and biosecurity on farms and in agricultural R&D. USDA maintains a comprehensive, systematic surveillance system to detect threats to plant health[38] and animal health[39]. USDA invests in development of veterinary biologics, vaccines, and other countermeasures. The USDA National Bio and Agro-Defense Facility[40] (NBAF) for large animals in Manhattan, Kansas, conducts foreign animal disease research, training, and diagnostics. NBAF is essential for research on diseases that can devastate animal agriculture, research that cannot safely take place elsewhere.

Recommended New Biosafety and Biosecurity Measures

The Biosafety and Biosecurity Innovation Initiative (BBII) will identify key areas for investment across the bioeconomy. In agriculture, these investments can improve identification of emerging pathogens. For example, a plant health defense facility analogous to NBAF would allow for advancement of research to protect U.S. crops from emerging pathogens and pests.

Opportunities for Public-Private Collaboration

Partnerships between private companies and academic institutions allow them to use a portion of their infrastructure for R&D and enable them to take advantage of existing knowledge to scale up new products. Such collaborations are critical in incentivizing investments, creating new jobs and market opportunities, and boosting sustainability.

Existing Public-Private Partnerships

Long-standing partnerships between USDA and Land Grant Universities (LGUs) and the Cooperative Extension System bring discoveries from laboratories to producers who can put knowledge into practice. The Foundation for Food and Agriculture Research (FFAR) matches public and private-sector investments to address agricultural challenges. USDA is advancing climate-smart agriculture and food systems through the Agriculture Innovation Mission for Climate (AIM4C), enabling global investments of over $8 billion with more than 300 partners. Domestically, USDA's Partnerships for Climate-Smart Commodities will provide $3.1 billion for public-private partnerships that provide technical and financial assistance to producers to implement climate-smart production practices.

Public-private partnerships also support targeted innovation. For example, the USDA Bioproducts Pilot Program[41] supports scale-up of bioproduct manufacturing through collaboration between academic institutions and private enterprises. The Germplasm Enhancement of Maize[42] (GEM) Project brings together LGUs and corn breeding companies to increase the diversity of U.S. maize germplasm. The Wheat Genetics Resource Center (WGRC) aims to unlock the genetic potential of wheat's ancient

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[38] Crop Biosecurity and Emergency Management | U.S. Department of Agriculture
[39] Animal Health Surveillance in the United States | U.S. Department of Agriculture
[40] National Bio and Agro-Defense Facility | U.S. Department of Agriculture
[41] Bioproduct Pilot Program | U.S. Department of Agriculture
[42] Germplasm Enhancement of Maize | U.S. Department of Agriculture

ancestors with input from an extensive advisory council. The Meat Animal Research Center[43] is a cooperative effort to solve high-priority problems for the beef, sheep, and swine industries. The P3Nano[44] partnership promotes use of cellulose nanomaterials derived from wood to reduce our dependence on greenhouse-gas-intensive materials like cement, plastic, and oil.

Opportunities for U.S. Government Incentivization of Private Sector

Strengthening existing and creating new partnerships will promote translation of research into products that meet challenges in food and agriculture. For example, USDA could establish an extramural program based on the Industry-University Cooperative Research Centers[45] program, which facilitates public-private collaborations for precompetitive R&D. Participating companies contribute $50,000 annually, participate in setting research priorities, can access information and intellectual property, and can license technologies either exclusively or well ahead of nonparticipating companies.

Stakeholders from the plant-breeding sector suggest that collaborations like GEM and WGRC could be initiated for other species, in which the private sector provides germplasm and in-kind support and the public sector leads "pre-breeding" efforts to diversify the species, with input from producers and manufacturers. Stakeholders from the alternative proteins sector suggest new Centers of Excellence that would innovate new products and processes, train the next-generation workforce, and enable information exchange between academia and the private sector through Industry Advisory Boards.

Opportunities for Public Participation

There will be opportunities for public participation as R&D programs are developed, such as R&D funding opportunities related to the goals in this report, as well as input at workshops, sessions at meetings, listening sessions, and Requests for Information.

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[43] U.S. Meat Animal Research Center | U.S. Department of Agriculture
[44] P3Nano – Advancing Commercialization of Cellulosic Nanomaterials | U.S. Endowment for Forestry and Communities
[45] Accelerating Impact Through Partnerships: Industry-University Cooperative Research Centers | National Science Foundation

Biotechnology and Biomanufacturing R&D to Further Supply Chain Resilience

In collaboration with other U.S. Federal Government departments and agencies, this report was authored by the U.S. Department of Commerce

Executive Summary

Recent global disruptions, geopolitical conflicts, and weather events exposed the vulnerability of U.S. supply chains critical for industrial production. Some companies were forced to overhaul operations and rethink their sourcing strategies for raw materials needed for essential goods including vehicles, airplanes, medical equipment, power generation, batteries, and catalytic converters.[46] New biotechnologies and biomanufacturing processes have the potential to help mitigate the risks and effects of supply chain disruptions. Synthetic biology can be used to replace existing production processes, such as for precursor materials, and to create new products, resulting in new opportunities for diversifying production pathways and alleviating supply chain chokepoints. For example, realizing biomanufacturing breakthroughs for active pharmaceutical ingredients (APIs) has the potential to create environmentally sustainable, domestic alternatives to API production, which is currently heavily concentrated abroad. Biotechnology and biomanufacturing can transform production of food, fuels, materials, and chemicals more broadly, creating flexible and adaptive platforms that not only mitigate disruption risks, but also enable producers to address disruptions more quickly. In the near-term, new developments in biotechnology platforms and advanced data analytics could enable manufacturers to pivot more efficiently and deliver multiple needed goods at scale compared to current production pathways. Industry analysis suggests that biological production applications could have direct economic impact of up to $4 trillion a year over the next 10 to 20 years.[47]

This report provides a vision for harnessing research and development (R&D) advances in biotechnology and biomanufacturing to build supply chain resilience. This vision is comprised of nine near- and long-term bold goals, and associated R&D needs, within three major themes. If this vision is achieved, the United States can bring innovative biotechnologies and products to markets faster while building a more robust supply chain ecosystem.[48]

In **Theme 1**, we provide bold goals for alternative supply chain pathways via biotechnologies and biomanufacturing to promote economic security. We identify R&D opportunities to promote the development of innovative biomanufacturing pathways that could address supply chain bottlenecks for critical drugs, chemicals, and other materials.

In **Theme 2**, we explore biomanufacturing innovation to enhance supply chain resilience. We identify R&D efforts required to advance flexible and adaptive biomanufacturing platforms to mitigate the effects of supply chain disruptions.

In **Theme 3**, we address standards and data infrastructure to support biotechnology and biomanufacturing commercialization and trade. We identify standards and data R&D needed to enable biotechnology and biomanufacturing scale-up and global competitiveness of U.S. companies.

Achieving these bold goals will require public-private partnerships, effective coordination with domestic and international partners, and integration of key biosafety and biosecurity considerations. Realization of these bold goals can also enable the United States to maintain its global leadership in the emerging bioeconomy and create quality jobs while addressing some of society's greatest challenges.

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[46] OECD Policy Responses on the Impacts of the War in Ukraine | Organisation for Economic Co-operation and Development
[47] The Bio Revolution: Innovations Transforming Economies, Societies, and Our Lives | McKinsey & Company
[48] Building Resilient Supply Chains, Revitalizing American Manufacturing, and Fostering Broad-Based Growth: 100-Day Reviews under Executive Order 14017 | White House

Bold Goals for Harnessing Biotechnology and Biomanufacturing

The following goals are intended to provide a broad vision to build supply chain resilience for the U.S. bioeconomy. These should not be read as commitments by the U.S. Department of Commerce (DOC) to undertake specific activities. Achieving these bold goals will require significant prioritization of R&D investments and efforts across the U.S. government, as well as actions from the private sector and state, local, and tribal governments.

Theme 1: Alternative Supply Chain Pathways via Biotechnologies and Biomanufacturing to Promote Economic Security

Goal 1.1: Improving Supply Chains for Critical Drugs – In 5 years, deploy broad synthetic biology and biomanufacturing capabilities to produce at least 25% of all active pharmaceutical ingredients (APIs) for small molecule drugs.

Goal 1.2: More Sustainable Chemical Production – In 20 years, produce at least 30% of the U.S. chemical demand via sustainable and cost-effective biomanufacturing pathways.

Goal 1.3: Accelerating Development of Biomanufactured Products – In 20 years, implement new biotechnologies into biomanufacturing workflows to produce ten new biomanufactured products in each of at least 3 sectors with identified supply chain bottlenecks.

Theme 2: Biomanufacturing Innovation to Enhance Supply Chain Resilience

Goal 2.1: Predictive Capabilities – In 5 years, enable prediction of at least 50% of supply chain weaknesses and direction of real-time biomanufacturing adjustments to address bottlenecks.

Goal 2.2: Real-time Biomanufacturing Process Adjustments – In 5 years, operationalize monitoring systems to measure and adjust biomanufacturing parameters in real time.

Goal 2.3: Adaptive Supply Chains – In 20 years, deploy a suite of advanced biomanufacturing platforms and capabilities to respond to supply chain bottlenecks within one week of identification.

Goal 2.4: Supply Chain Flexibility – In 20 years, implement 80% of viable biomanufacturing technologies to address domestic production capability needs.

Theme 3: Standards and Data Infrastructure to Support Biotechnology and Biomanufacturing Commercialization and Trade

Goal 3.1: Data Infrastructure – In 5 years, launch a data infrastructure, including effective and secure data sharing mechanisms, via advances and integration of data standards, tools, and capabilities.

Goal 3.2: Standards Infrastructure – In 20 years, establish a robust standards infrastructure to enable the rapid development and deployment of biomanufactured products and processes.

Bold Goals Explored

Theme 1: Alternative Supply Chain Pathways via Biotechnologies and Biomanufacturing to Promote Economic Security

Context for the Bold Goals

Biomanufacturing, part of the Administration's priority in advanced manufacturing, can be utilized to make products to mitigate existing and future supply chain bottlenecks.[49] Biotechnology innovations can create new processes to make products ranging from active pharmaceutical ingredients to biofuels, chemicals, plastics, enzymes, critical materials, and beyond. State-of-the-art biomanufacturing facilities can lead to long-term production cost savings and transform domestic manufacturing to be more sustainable and reduce environmental impacts compared to traditional production pathways. For some products, the biotechnologies already exist to address high-risk bottlenecks, and public-private partnerships must focus on de-risking technology deployment and expansion. Other biotechnologies are more nascent, and public investment must focus on translating them from R&D to biomanufacturing practice. Doing so will help enable a more secure, sustainable, diversified, and resilient supply chain—from locally sourced feedstocks at the beginning, through manufacturing processes, to market-viable goods. Goals 1.1 through 1.3 aim both to replace at-risk products with biomanufactured goods where the technology has already demonstrated potential viability and to develop new biomanufactured products to diversify and replace supply chain inputs, including in sectors where biomanufacturing is not currently utilized or is underutilized.

Goal 1.1: Improving Supply Chains for Critical Drugs. Biomanufacturing can help address the risk of domestic dependence on concentrated geographies for active pharmaceutical ingredients (APIs). Currently, most APIs of small molecule drugs are synthesized through a chemical process abroad, including in China and India, which poses supply chain risks.[50] There have been relatively low financial incentives for reshoring these chemical manufacturing processes, especially for production of molecules with low profit margins. Biomanufacturing pathways would create opportunities for cost-effective domestic API production. For example, advances in synthetic biology, including in precision fermentation and the use of cell-free systems, could enable firms to produce multiple APIs in the same facility, with a reduced need for retooling. Additional proof of concept at scale is needed to help overcome private sector hesitancy to invest in adaptive and flexible technologies with long-term potential.

Goal 1.2: More Sustainable Chemical Production. Biomanufacturing has the potential to transform U.S. chemical manufacturing by reducing reliance on fossil fuels and advancing domestic production. Biomanufacturing production, extraction, recycling, and upcycling are already replacing supply chain staples such as fuels, solvents, enzymes, and plastics; however, there is opportunity to expand. The biobased products industry directly added $150 billion to the U.S. economy in 2017, while biobased chemicals and enzymes contributed an additional $6.2 and $21.7 billion, respectively.[51] A well-developed bioeconomy could use more than one billion tons of sustainable biomass and biogenic carbon in the United States within the next 20 years.[52] Bulk chemicals produced from biomass can help the United States avoid both the carbon impacts of traditional feedstocks and the price volatility of commodity feedstocks. To produce 30% of U.S. demand of chemicals with biomass, R&D must be expanded beyond current capabilities and focused on production, transportation, and pre-processing of biomass, and on improving downstream processing and precision fermentation capabilities.

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[49] National Strategy for Advanced Manufacturing | National Science and Technology Council

[50] Building Resilient Supply Chains, Revitalizing American Manufacturing, and Fostering Broad-Based Growth: 100-Day Reviews under Executive Order 14017 | White House

[51] Indicators of the U.S. Biobased Economy, 2018 | U.S. Department of Agriculture

[52] 2016 Billion-Ton Report | U.S. Department of Energy

Goal 1.3: Accelerating Development of Biomanufactured Products. Recent advances in synthetic biology and artificial intelligence (AI) are leading to new breakthroughs for the bioeconomy. Biotechnology innovation can provide access to new classes of molecules currently inaccessible using traditional chemistry, driving new applications and opportunities for economic growth. For example, biotechnologies could enhance the domestic supply chain for critical minerals, which is currently insufficient to support reshoring and expansion of the semiconductor industry. Additionally, biomass can serve as a dynamic feedstock for drop-in fuels in hard-to-abate sectors such as aviation and marine shipping. Strategic investments must be made to translate these biotechnology breakthroughs into large-scale production, including developing methods to help recover valuable commodity chemicals and materials from discarded devices and other waste streams for transitioning back into the supply chain. If successful, this will reduce the dependence on fossil fuels and non-domestic sources of critical chemicals and materials while helping to meet the Administration's climate and sustainability goals.

R&D Needs

- Develop cost-competitive alternative biomanufacturing pathways, such as cell-based processes and cell-free systems, to produce key APIs, chemicals, and other materials. **(Goals 1.1, 1.2, 1.3)**
- Design and test sustainable and cost-effective manufacturing capabilities and capacities to support large-scale biomanufacturing for commodity material production. **(Goals 1.2, 1.3)**
- Advance synthetic biology tools and innovative bioprocessing means to reclaim/harvest critical minerals, including, but not limited to, lithium and cobalt. **(Goal 1.3)**
- Conduct lifecycle cost analyses to determine the most economically viable model(s) for biomanufacturing while ensuring biosafety, biosecurity, and biocontainment. **(Goals 1.1, 1.2, 1.3)**
- Develop lifecycle management practices to enable more sustainable biomanufacturing and develop biomanufacturing solutions for advancing the circular (bio)economy via recycling or upcycling of existing products and other wastes or byproducts. **(Goals 1.2, 1.3)**
- Develop models to predict the most promising chemical production processes where biomanufacturing alternatives can produce equal or greater scale or quality while maximizing sustainability. **(Goals 1.1, 1.2, 1.3)**
- Improve accessibility to platform technologies for engineering biology with AI to speed and optimize R&D and scaling of new processes and products. **(Goals 1.1, 1.2, 1.3)**
- Address current scale-up challenges and regulatory science needs. **(Goals 1.1, 1.2, 1.3)**

Theme 2: Biomanufacturing Innovation to Enhance Supply Chain Resilience

Context for the Bold Goals

An advanced biomanufacturing ecosystem has the potential to mitigate disruptions, but also to adapt when inevitable shortages occur. U.S. stakeholders have emphasized the need for increased data and models to predict potential bottlenecks, such as disruptions in shipping routes or shortages of materials. A more advanced supply chain predictive capability could provide manufacturers with enough time to shift or pre-position assets and inventories to prevent bottlenecks. Further, biomanufacturing can offer agile platforms and workflows that can be used to quickly shift from the production of one good to another without major infrastructure changes. Goals 2.1 through 2.4 lay the foundation for this resilient production ecosystem, so that the United States and international partners can expand advanced biomanufacturing capabilities, including more regional biomanufacturing close to feedstocks.

Goal 2.1: Predictive Capabilities. Some supply chain disruptions are unavoidable, whether due to geopolitical conflict, transportation delays, public health emergencies, weather-related disasters, or production errors. Regardless of the disruption type, both the private and public sectors must better understand supply chain sources and feedstocks, as well as their relationships on interconnected supply chains. A data-driven understanding of supply chain dependencies will help enable stakeholders to prepare for and mitigate the effects of shocks. Technological tools, including access to data and deploying machine learning and AI, can enable government and firms to map supply chains, identify risks, and invest in biomanufacturing capabilities to address those risks. In the long-term, real-time data could be used to flag emergent risks, enabling manufacturers to maintain their economic viability while pivoting production for continued delivery of necessary goods to consumers.

Goal 2.2: Real-Time Biomanufacturing Process Adjustments. Biomanufacturing using living cells may be more variable than traditional chemical manufacturing, requiring advanced monitoring systems to better control quality and yield. Real-time monitoring and process control of bioreactor processes, such as fully enclosed fermentation systems, are needed to enable real-time quality control. To provide real-time monitoring of living organisms at scale, emerging biotechnology-based solutions should be considered. For example, reporter cell lines and organisms containing genetic sensors that can provide readouts on specific biological responses could address current analytical bottlenecks. Such monitoring and process control innovations can help manufacturers understand production problems and adjust relevant parameters more quickly, resulting in added biomanufacturing efficiencies toward achieving resilient supply chains.

Goal 2.3: Adaptive Supply Chains. Advanced biomanufacturing platforms and capabilities fueled by biotechnology innovation and increased connectivity, automation, and data analytic capabilities have the potential to create more agile and sustainable products faster. In the face of supply chain disruptions, manufacturers could shift production more efficiently, including in coordination with international partners, rather than undergoing capital-intensive retooling. These developments would also provide customizable options to make different products as demand shifts while building supply chain redundancy and flexibility. However, limited investments have been made toward the development of advanced biomanufacturing technologies. A robust set of biotechnologies, including bioreactors, raw materials and reagents, and measurement capabilities would enable the United States to quickly address supply chain bottlenecks using a diversified set of technology solutions, including better access and utilization of raw materials.

Goal 2.4: Supply Chain Flexibility. Large-scale production of new biotechnology products requires a robust global manufacturing ecosystem and infrastructure. The most functional and economical way to expand the biomass-to-chemicals industry is to locate biomass processing facilities close to feedstock production. Such co-localization can promote economic growth across the Nation, strengthen resilience to domestic supply chains, and address the policy goal of revitalizing the economies of rural communities, as well as those facing hardships associated with the loss of traditional manufacturing jobs. To promote a robust biomanufacturing ecosystem, investments are needed to develop and implement fit-for-purpose manufacturing platforms, including modular and/or mobile platforms, for converting biomass, enzymes, metabolites, and other sources into viable products. Importantly, biomanufacturing technologies must keep pace with rapid biotechnology innovations to produce a diverse product portfolio for multiple sectors. Additionally, continued improvement in biomanufacturing technologies is necessary to make processes cheaper, more efficient, and more sustainable.

R&D Needs

- Develop predictive models to identify the supply chain bottlenecks that would benefit most from biomanufacturing alternatives (such as high-demand commodity chemicals or materials) and models to forecast market trends and workforce needs (such as skills, geography, and permanent and surge capacity) to address biomanufacturing and supply chain bottlenecks. **(Goal 2.1)**
- Develop accurate models to integrate a decentralized or distributed biomanufacturing ecosystem and supporting information technology infrastructure, including a map of domestic capacities, and to predict the availability and use impacts of biological feedstocks to enable on-demand local production. **(Goals 2.1, 2.3, 2.4)**

- Develop innovative in-line, at-line, and in-process measurement technologies, including engineered reporter cell lines and living measurement systems, to enable real-time evaluation of and adjustments to quality attributes. **(Goal 2.2)**
- Develop datasets, standards, and predictive capabilities (including use of AI, machine learning, and digital twins) to enable real-time feedback loops and analysis of process control and supply chain data with appropriate access controls and data security. **(Goal 2.2)**
- Advance smart biomanufacturing that can seamlessly integrate automation, software, equipment, and people to increase process speed, reliability, and efficiency. **(Goals 2.2, 2.3)**
- Develop platform technologies and standards to accelerate the development, production, and interoperability of biomanufacturing equipment, components, and consumables and improve the characterization and testing of biomanufacturing processes and products. **(Goals 2.3, 2.4)**
- Develop standard sets of microbial strains, cell free systems, key reagents, sequences of known function and performance, and supply chain precursor molecules and compounds that can be rapidly produced, distributed, and scaled up on demand. **(Goals 2.3, 2.4)**
- Develop standardized quality metrics for raw materials and reagents to enable interoperability from multiple vendors, and advanced algorithms to enable adaptive stockpiling capable of using alternative feedstocks or processes when supply chains are limited or disrupted. **(Goals 2.3, 2.4)**
- Develop innovative design, robust quality management systems, and standards to enable more efficient use of biomanufacturing facilities. **(Goals 2.3, 2.4)**
- Develop technologies and related strategies that can be used to effectively retrofit existing facilities for biomanufacturing in urban and rural areas. **(Goals 2.3, 2.4)**
- Develop modular biomanufacturing capabilities to be scaled up, down, or out. **(Goals 2.3, 2.4)**
- Develop single-use technologies and both fit-for-purpose and end-to-end biomanufacturing platforms that can quickly switch between organisms and processes. **(Goals 2.3, 2.4)**

Theme 3: Standards and Data Infrastructure to Support Biotechnology and Biomanufacturing Commercialization and Trade

Context for the Bold Goals

Stakeholder reports and global bioeconomy strategies recognize that a sustainable, safe, and secure bioeconomy is built upon standards and the availability of high-quality data.[53,54] Data, particularly from genomics and multiomics, underpins advances in biotechnology, for example, by enabling the rapid design of systems to produce needed medicines, food, and materials. Standards,[55] particularly international standards, can help accelerate R&D and commercialization of new, safe, and effective medicines and therapeutics; contribute to food product safety, quality, and consistency; promote international trade; and instill confidence among consumers for products in all sectors of the economy. For industry, standards can promote research and manufacturing innovation, streamline regulatory review, and enable international alignment, interoperability, and coordination. As biotechnology converges with automation, connected devices, and AI, a robust data infrastructure can also accelerate R&D and commercialization of emerging technology.[4,5] The Administration's Data for the Bioeconomy Initiative (Data Initiative) under Section 4 of the Executive Order will help inform these efforts.

Goal 3.1: Data Infrastructure. A standardized data infrastructure to connect and integrate various biological data types, including those associated with biomanufacturing, can accelerate biotechnology and biomanufacturing innovations, such as understanding the efficacy and toxicity of a drug and how each can be affected by the manufacturing process. To better leverage the large amount of data generated from

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[53] The U.S. Bioeconomy: Charting a Course for a Resilient and Competitive Future

[54] European Bioeconomy Policy: Stocktaking and Future Developments | European Commission, Directorate-General for Research and Innovation

[55] Standards can include documentary standards, reference materials, and reference data.

R&D investments, the United States and international partners can work to develop tools, capabilities, and standards in accordance with Findable, Accessible, Interoperable, and Reusable (FAIR) principles. An open data infrastructure would enable R&D data to be aggregated and analyzed to drive innovation. For example, combining data related to genomics, protein structures, and biological functions has expedited the development of SARS-CoV-2 vaccines. Synergy from interdisciplinary collaborations, enabled by an open data architecture, could accelerate R&D, scale-up, and biomanufacturing processes.

Goal 3.2: Standards Infrastructure. As the United States expands its manufacturing capacities, there is an increasing need to develop pre-competitive technologies, ensure a level playing field for both domestic and multinational companies, and reduce barriers to market access. The United States can support growth of a bioeconomy through continued leadership in and development of international standards, including in emerging biotechnologies (e.g., synthetic biology) and biomanufacturing. For example, standard manufacturing processes, testing methods, raw materials, and data can support agile manufacturing to mitigate the effects of supply chain bottlenecks and ensure quality production. A holistic, global approach to a sustained standards infrastructure that keeps pace with rapidly evolving biotechnology will catalyze innovations and accelerate bioeconomy growth. Continued investment is needed to develop dissemination and educational tools are needed to drive industry adoption of the latest standards.

R&D Needs

- Support development and integration data standards, tools, and capabilities to create a data infrastructure consistent with the Administration's Open Science efforts[56] while respecting intellectual property rights, data security, and other needs in continuous coordination with domestic and international stakeholders. **(Goal 3.1)**
- Create data standards (e.g., ontology, schema, and metadata structure) to enable development, integration, and utilization of advanced data analytics, including AI and machine learning, and for operationalizing digital twin approaches. **(Goals 3.1, 3.2)**
- Establish benchmarks and tools for validating or verifying materials, systems, processes, equipment, software, and data for both lab-based and field-based technologies. **(Goal 3.2)**
- Develop analytical method standards and the underpinning measurement infrastructure to enable greater comparability of complex biological systems. **(Goal 3.2)**
- Develop bioprocessing standards to support emerging biomanufacturing capabilities, including for raw materials, unit operations, bioreactors, and related interoperability. **(Goal 3.2)**
- Translate industry benchmarks, tools, capabilities, and best practices into international standards in collaboration with Manufacturing USA institutes and other open forums to ensure that standards promote, and do not inadvertently stifle, innovation. **(Goal 3.2)**

Stakeholder Consultation

To develop this report, DOC leveraged existing industry and government analyses and consulted with public and private sector stakeholders. This included participation in listening sessions organized by the White House and workshops such as the National Academies of Sciences, Engineering, and Medicine's "Successes and Challenges in Biomanufacturing."[57] DOC also reviewed responses to the Request for Information on the National Biotechnology and Biomanufacturing Initiative and collaborated with experts from multiple Federal agencies.[58]

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[56] Fact Sheet: Biden-Harris Administration Announces New Actions to Advance Open and Equitable Research | White House
[57] Successes and Challenges in Biomanufacturing – A Workshop | National Academies of Sciences, Engineering, and Medicine
[58] Request for Information on the National Biotechnology and Biomanufacturing Initiative | Office of Science and Technology Policy

Enhancing Biosafety and Biosecurity

To realize the potential of biotechnology and biomanufacturing to promote U.S. economic growth and enhance supply chain resilience, it is imperative that biosafety and biosecurity are integrated into both biotechnology R&D and implementation strategies for newly adopted biomanufacturing processes.

Existing Biosafety and Biosecurity Measures

The United States has decades of experience in implementing biosafety and biosecurity measures, as will be outlined in the forthcoming plan for the Biosafety and Biosecurity Innovation Initiative established through the Bioeconomy Executive Order. Although most evident in the health sector and at laboratories with biological materials at the highest biosafety levels, systems and cultures throughout the bioeconomy R&D enterprise have been developed and cultivated through training and education provided by the U.S. government, universities, and professional societies such as ABSA International. Several Federal agencies engage in outreach domestically and internationally to propagate biosafety and biosecurity best practices. Expanding upon this robust foundation is critical as biotechnology and biomanufacturing are used to enhance supply chain resilience across sectors that do not have the same historical biosafety and biosecurity standards.

Recommended New Biosafety and Biosecurity Measures

Themes 1 and 2 involve developing, implementing, and scaling up new biotechnologies and biomanufacturing processes to serve as alternatives to more conventional production pathways. By default, the implication is that biological materials and systems will be utilized in new ways while being engineered to make both new and familiar products. Biosafety and biosecurity should be included in these new technologies and processes early in the design phase (including for living systems and their interactions with more traditional manufacturing equipment), during hardware and software integration, and through intentional assessments to monitor for new risks, gaps, or challenges.

Themes 2 and 3 emphasize the importance of data for supply chain resilience. Best practices for data management and protection should be enacted, including concepts such as those within the National Institute of Standards and Technology (NIST) Research Data Framework and the NIST Cybersecurity Framework. These practical guides can help end users work through the balance of utilizing open or shared supply chain data while securing the more vulnerable data results from predictive modeling that indicate specific supply chain risks and opportunities.

Theme 3 centers on standards development to help increase the use of promising biotechnology and biomanufacturing developments to improve supply chain resilience. Each of the referenced standard types (documentary standards, data standards, and reference materials) should be developed to ensure the integration of biosafety and biosecurity best practices. This includes for administrative, engineering, and access controls; handling of potential dual-use biological materials; and critical infrastructure hardening. Doing so will help realize the economic benefits possible through increased adoption of biotechnologies and biomanufacturing innovations while minimizing risks as the biotechnology workforce expands.

Opportunities for Public-Private Collaboration

Achieving this vision for supply chains requires a coordinated and concerted effort to overcome shared challenges between Federal, state, local, and tribal governments, and the private sector. A key barrier that stakeholders have emphasized is a severe lack of domestic biomanufacturing infrastructure for the pilot and commercial scales. To test or to manufacture products at scale, many companies must seek options abroad, which still pose long wait periods, or invest in the infrastructure themselves. This is an onerous endeavor for a startup with limited capital and production know-how. If these hurdles persist, the United States may miss a rare opportunity to innovate while strengthening its supply chains. Public-private partnerships (PPPs) have the potential to drive commercialization and enhance broader supply chain resilience, including if coupled with policymaking and investment incentives at the local, state, and/or

Federal level. Such efforts can drive the translation of emerging biotechnologies into practical applications; promote technology development, support, and deployment; increase access to pilot and test capabilities; build capacity; and develop and train a robust workforce.

The President's Council of Advisors on Science and Technology has recommended the development of biomanufacturing infrastructure hubs across America to advance manufacturing methods for complex new bioproducts and provide workforce development opportunities.[59] The power of PPPs lies in the cohesive network of stakeholders, coming together to enable tangible demonstrations of technology, capabilities, and concepts with collective effort. Pilot biotechnology demonstrations require substantial supply chain considerations, such as raw materials, infrastructure needs, circular production considerations, and market fit. Shared facilities operated in the pre-competitive space may improve or expand laboratory infrastructure, including state-of-the-art piloting and scale-up facilities, to enable the demonstration of engineering biology metrology and bioeconomy standards, demonstrate pre-competitive technologies, pressure-test supply chain considerations in an industry-representative environment, and provide a platform for training opportunities and workforce development. These types of hubs and collaborations can significantly de-risk the investments needed to develop and integrate new biotechnologies and biomanufacturing processes, including through decreased costs for capitalized equipment, increased use of common platform technologies to scale up new pathways, and improved clarity on the viability of biomanufactured products in one or more economic sectors.

Existing Public-Private Partnerships

DOC is well-poised to lead and participate in such PPPs. Intended to boost economic recovery from the pandemic and rebuild American communities, the Economic Development Administration's (EDA) Build Back Better Regional Challenge led in part to investments in biomanufacturing research centers across the country. EDA's Regional Technology and Innovation Hubs program is intended to drive technology- and innovation-centric growth that leverages existing R&D strengths and technology demonstration and deployment capacities within a region to catalyze the creation of good jobs for American workers equitably and inclusively. The Small Business Innovation Research and Small Business Technology Transfer programs encourage technology commercialization by domestic small businesses. The national network of Manufacturing USA institutes was created to secure U.S. global leadership in advanced manufacturing through large-scale public-private collaboration to overcome technical hurdles, share state-of-the-art facilities and equipment, and train tomorrow's workforce. The National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL), BioFabUSA, and BioMADE target biomanufacturing, while other institutes can also drive relevant advancements. The network of Manufacturing Extension Partnership centers in every state and Puerto Rico serves small and medium-sized manufacturers to optimize supply chains, deploy new technologies, and train and recruit talent, among other services. Via consortia like Rapid Microbial Testing Methods, Genome Editing, Flow Cytometry Standards, and Genome in a Bottle, NIST works with industry and international partners to lay the foundation for developing research, standards, capacities, and expertise for supporting biotechnology and biomanufacturing.

Opportunities for U.S. Government Incentivization of Private Sector and Public Participation

The Federal Government can support biotechnology and biomanufacturing commercialization via unique lab-to-market incentive mechanisms. Proven tools to address market failure and applied technologies gaps include prize and challenge competitions, market shaping procurement or loan programs, and streamlined funding of open, cross-disciplinary research. A new PPP could coordinate across multiple efforts to ensure they drive toward rapid technology assimilation and execution. Under **Themes 1 and 2**, PPPs can

[59] Biomanufacturing to Advance the Bioeconomy | President's Council of Advisors on Science and Technology

help address challenges in technology demonstration, process development, and continuous optimization by seeding a bioproduction R&D shared facility network. As a starting point, this could occur across at least four geographical locations to offer bioprocess optimization capabilities to the greater bioeconomy and execute pilot and scale-up challenges wherein participating facilities would compete in areas such as workflow optimization, scaling, and transfer. Generated data could be captured in an open data infrastructure **(Theme 3)** and support generation of supply chain predictive models **(Theme 2)**. PPPs could provide participants access to neutral forums for addressing pre-competitive needs through (1) public workshops; (2) participation in development of experimental benchmarks, guidelines, standards, technologies, manufacturing platforms, equipment, and facilities to build competence; (3) access to co-developed tools, capabilities, and expertise; and (4) institutional representation on consortia committees.

Biotechnology and Biomanufacturing R&D to Further Human Health

In collaboration with other U.S. Federal Government departments and agencies, this report was authored by the U.S. Department of Health and Human Services

Executive Summary

Improvements in human health outcomes have benefited from advances in biotechnology and biomanufacturing over the last two centuries, from the discovery of genetics and the development of early vaccines to modern robotic limbs and engineered cell therapy. To prevail in the fight against disease and strive toward healthy living, several emerging fields in biotechnology and biomanufacturing need to be strengthened and developed further. In taking these key steps, the U.S. government, in collaboration with the private sector, can advance areas throughout the full health continuum—from prevention to diagnosis and monitoring, to more efficient therapeutic manufacturing, to therapy and ultimately healthy survivorship. This report describes ten aspirational bold goals under five broad themes that will accelerate medical breakthroughs and advance human health. The report also details important research and development necessary to work toward the bold goals.

Theme 1, **accessible health monitoring**, includes bold goals to identify indicators of health and develop and distribute a simple-to-use home diagnostic assay kit to report health across the lifespan and meet the needs of diverse populations. This theme focuses on prevention, monitoring, and survivorship.

Theme 2, **precision multi-omic medicine**, includes bold goals to collect multi-omic measures in large cohorts with diverse populations, as well as to develop molecular classifications for diagnosis and/or treatment and make these actionable with development of the $1,000 multi-ome. This theme focuses on enabling diagnosis and monitoring as well as survivorship.

Theme 3, **biomanufacturing of cell-based therapies**, includes bold goals to expand the toolset of technologies used to create cell-based therapies to achieve high viability and targeted delivery at the time of patient administration, as well as expand access to cell-based therapies to decrease health inequities. This theme focuses on equitable access to next-generation therapy.

Theme 4, **AI-driven bioproduction of therapeutics**, includes bold goals to increase the speed and diversity of therapeutic manufacturing, including manufacture of current therapeutics as well as design of novel ones. This theme focuses on enabling broad access to advanced therapeutics.

Theme 5, **advanced techniques in gene editing**, includes bold goals to assess current gene-editing systems and emerging technologies for therapeutic gene editing as well as to strengthen the biomanufacturing ecosystem to produce millions of doses of therapeutic gene-editing systems annually. This theme focuses on enabling new therapeutics.

All these topic areas and their component bold goals require continued support for R&D and establishment of public-private partnerships as well as consideration of biosafety and biosecurity. The goals require innovation across the biotechnology development spectrum, from basic science and prototyping to validation, clinical studies, manufacturing, and commercialization, culminating in regulatory approval and health insurance authorization and reimbursement. Also, building in sound biosafety and biosecurity practices that preserve critical discovery and innovation is a key component of the development of all referenced biotechnologies. This enables safe solutions to human health challenges and is a critical factor that must be considered in the design and implementation of programs that might be pursued to achieve these goals. In summary, these bold goals are designed to accelerate emerging fields in biomedicine for the benefit of Americans by increasing the quality of life of people across their lifespans through advancements in biotechnology and biomanufacturing.

Bold Goals for Harnessing Biotechnology and Biomanufacturing

The following goals in the advancement of human health are intended to provide a broad vision for the U.S. bioeconomy. These should not be read as commitments by the U.S. Department of Health and Human Services to undertake specific activities. Achieving these bold goals will require significant prioritization of R&D investments and efforts across the U.S. government as well as actions from the private sector and state, local, and tribal governments.

Theme 1: Accessible Health Monitoring

Goal 1.1: Identify Bio-Indicators of Health – In 5 years, leverage novel sensors to identify at least ten next-generation bio-indicators of health that can be monitored as part of standard healthy living and preventative medicine practice, such as immune competency or microbiome composition.

Goal 1.2: Integrated Health Diagnostics – In 20 years, develop and distribute a simple-to-use, affordable home diagnostic assay kit ("Health Kit") leveraging novel bio-indicators of health, useful in the clinic and community, and meeting the needs of diverse populations to decrease disparities in health outcomes by 50%.

Theme 2: Precision Multi-Omic Medicine

Goal 2.1: Collect Multi-Omic Data – In 5 years, collect multi-omic measures in large cohorts with participants from diverse populations and identify which measures are most relevant to the diagnosis and management of at least 50 diseases with high incidence and impact.

Goal 2.2: Enable Personal Multi-Ome – In 20 years, develop molecular classifications for diagnosis, prevention, and treatment to address leading causes of disease-related mortality in the U.S. and make these actionable with development of the $1,000 multi-ome.

Theme 3: Biomanufacturing of Cell-Based Therapies

Goal 3.1: Increase Therapeutic Efficacy – In 5 years, expand the technologies used to develop cell-based therapies to achieve at least 75% cell viability in patients.

Goal 3.2: Enable Scale-Up – In 20 years, increase the manufacturing scale of cell-based therapies to expand access, decrease health inequities, and decrease the manufacturing cost of cell-based therapies 10-fold.

Theme 4: AI-Driven Bioproduction of Therapeutics

Goal 4.1: Increase Manufacturing Speed – In 5 years, leverage a national network of resource labs to address barriers in autonomous production and bioproduction of existing biotherapeutics, increasing manufacturing speed of ten commonly prescribed therapeutics by 10-fold.

Goal 4.2: Increase Manufacturing Diversity – In 20 years, integrate artificial intelligence and machine learning (AI/ML) into the national network of resource labs to design novel biotherapeutics, increasing the speed of novel drug discovery and production by 10-fold.

Theme 5: Advanced Techniques in Gene Editing

Goal 5.1: Increase Editing Efficiency – In 5 years, further develop gene-editing systems for clinical use to enable, with little to no side effects, cures for ten diseases with known genetic causes.

Goal 5.2: Enable Scale-Up – In 20 years, strengthen the biomanufacturing ecosystem to produce at least 5 million doses of therapeutic gene-editing systems annually.

Bold Goals Explored

Theme 1: Accessible Health Monitoring

Context for the Bold Goals

A major healthcare challenge is detecting and monitoring disease early so prevention, progression, and treatment are manageable. This is especially true in areas with difficult access to healthcare and populations underrepresented in clinical studies. Identification of next-generation indicators of health in diverse populations that can be simply monitored at home or in community clinic settings could help address this issue, giving clinicians and patients a way to assess and monitor health and disease more effectively and affordably. These indicators can include known biomarkers with currently unknown clinical implications, as well as new biomarkers relevant to the function of human systems that are still difficult to monitor or measure, such as the immune system or the microbiome. Under this paradigm, healthcare providers and patients could use a new set of tools to organize, track, personalize, and prioritize patient care, enabling earlier diagnosis no matter the distance from a healthcare provider via telemedicine integration, testing of developmental therapeutics, and identification of ways to improve health across diverse populations. The bold goals for achieving this include a need to identify novel next-generation bioindicators of health as well as a need to enable integrated health diagnostics in a variety of care settings.

R&D Needs

The following aspects of R&D could be pursued in consultation with the National Institutes of Health (NIH), the Biomedical Advanced Research and Development Authority (BARDA), the Food and Drug Administration (FDA), the Centers for Medicare and Medicaid Services (CMS), and other government stakeholders.

To discover next-generation bioindicators of health **(Goal 1.1)**:

- Develop innovative sensors and sensor arrays for detection of novel bioindicator types.
- Combine longitudinal studies with studies of basic human biology to identify markers of health and healthy aging, requiring development of relevant AI/ML models to integrate data types.
- Integrate social and clinical studies on diverse population sets, including race, gender, and geographic area, into biomarker discovery to understand inequities, gaps in accessibility and affordability to health technologies, and biomarker diversity.
- Work closely with decentralized clinical studies and industry partners to design and launch new models for large-scale studies that can enable next-generation biomarker discovery and validation.
- Harmonize, integrate, and analyze Electronic Health Record (EHR) data across the many existing platforms to identify health biomarkers and enable interoperability. Other sections of this report refer to the challenges of data collection, curation, and storage within data infrastructures, but for this theme a specific infrastructure is required to handle mixed patient data from multiple sources while ensuring the security and protection of sensitive biological data and considering issues of privacy and deidentification.

To develop integrated health diagnostics **(Goal 1.2)**:

- Develop miniature detectors and sensors as well as advanced yet simple-to-use multiplexed detection panels, building on existing studies including those against cancer (part of the Cancer Moonshot℠ initiative[60]) and COVID-19 (part of the RADx® program[61] and BARDA DRIVe).
- Coordinate and consult with FDA and CMS for guidance in development and clinical use of Health Kits.
- Create specific partnerships with experts in public health, nursing, patient advocacy, and many others to ensure Health Kits are designed for accessible and affordable use by all Americans. Many partnerships are already in place to inform other efforts (such as RADx Tech for Accessible Tests[62]) as well as a coordinated distribution infrastructure. This could be informed by the infrastructure built to distribute home tests during the COVID-19 pandemic.
- Advance the validation and commercialization of novel wearable remote sensors, electronic health records (EHRs), and other sources of physiological data, potentially building on existing programs, such as those established by BARDA DRIVe, to predict vulnerability to disease and monitor for long term consequences.
- Consider data infrastructure for Health Kits, including how the data could be used to enable health improvement and be shared with a primary care provider or other clinician while still emphasizing protection of patient privacy and data security.

Theme 2: Precision Multi-Omic Medicine

Context for the Bold Goals

Precision medicine is an approach for disease prevention, diagnosis, and treatment that considers people's individual variations in genes, environment, and lifestyle.[63] Reductions in the cost of sequencing a human genome to <$1,000[64] has enabled DNA sequences to be incorporated into large-scale precision medicine initiatives (e.g., UK Biobank, All of Us ℠ Research Program, 100+ Cohort Consortium), studies of rare disorders (e.g., UDN, GREGoR, IRDIC), and studies of cancer in a rapid and cost-effective manner. This ability to directly measure, annotate, and interpret DNA sequence variation has transformed the approach to disease biology. Similarly, the addition of multi-omics technologies (e.g., epigenomics, transcriptomics, proteomics, metabolomics) into large cohorts with participants from diverse populations is poised to have similar transformational impacts on understanding and managing human health and disease. Major efforts such as The Cancer Genome Atlas[65] have used multi-omic data to characterize the molecular basis of cancer and demonstrate how that information can change the way patients are treated in the clinic—an approach also taken by programs supported by the Cancer Moonshot initiative.[66] A multi-omics approach could allow improved diagnosis and therapy options for patients, enabling classification of disease on a molecular basis combined with environment and lifestyle factors within a precision medicine paradigm. Achieving this medical paradigm at a large and equitable scale requires biotechnologies and biomanufacturing innovations to integrate multi-omic information in standard clinical practice. The bold goals for achieving this include collection of multi-omic data, as well as enabling of the personal multi-ome, with a focus on representation of diverse populations.

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[60] Cancer Moonshot℠ | National Cancer Institute
[61] Rapid Acceleration of Diagnostics (RADx) | National Institutes of Health
[62] RADx® Tech Accessible At-Home COVID-19 Tests | National Institutes of Health
[63] The Precision Medicine Initiative | National Institutes of Health
[64] The Cost of Sequencing a Human Genome | National Human Genome Research Institute
[65] Outcomes and Impact of The Cancer Genome Atlas | National Cancer Institute
[66] Generation of Human Tumor Atlases | National Cancer Institute

R&D Needs

To collect multi-omic data **(Goal 2.1)**:

- Develop novel sensors, such as *in vivo* DNA-based recorders, that allow for more passive longitudinal collection of data to enhance the widespread adoption of multi-omics approaches.
- Drive down costs through targeted investment in novel high-throughput technologies, including synthetic biology and cell-free approaches, with emphasis on enabling multi-omics characterization with spatial resolution throughout tissues for <$1000 per sample.

To enable the personal multi-ome **(Goal 2.2)**:

- Develop robust standards and benchmarks for multi-omics in consultation with agencies that support the development of diagnostic tools (e.g., NIH and BARDA) and those that approve and support diagnostic assays for use (e.g., FDA and CMS).
- Develop multi-omic data security and use covenants to protect patient privacy.
- Develop transformational approaches for assimilating, sharing, and analyzing complex multi-omic data types from lab values to EHR data, including improved methods for data visualization while ensuring data protection and security.
- Create standardized multi-omic data-collection and analytical approaches that enable predictive models.
- Develop clinical research methods integrating multi-omics with environmental, lifestyle, and other phenotypic data to enable clinically actionable patient classification, diagnosis, and therapy.

Theme 3: Biomanufacturing of Cell-Based Therapies

Context for the Bold Goals

Engineered cell-based therapy represents a new and exciting paradigm in therapeutic design, presenting new options to patients with severe diseases (such as cancer) who, in some cases, can be limited to traditional types of therapies with little hope of success. Perhaps the best-known cell-based therapies that have reached widespread clinical use are for cancer, including chimeric antigen receptor T (CAR-T) cells for certain hematological malignancies. CAR-T cells[67] have received six FDA approvals and have reached greater accessibility, enabling 40% durable remissions in patients with certain cancers. To reach its full potential, the method of manufacturing must be shortened, since the manufacturing time for certain CAR-T cell products average around 2 weeks. Also, the current manufacturing method incurs low availability, difficult harvesting of cells from each patient, shipping challenges, and difficulty in identifying patients who are likely to benefit from the treatment, which results in extremely high costs. All these challenges, coupled with the high potential for therapeutic efficacy in patients with few options, point to the need for a concerted effort to change the manufacturing of cell-based therapies. The bold goals for achieving this include focusing on increasing therapeutic efficacy of cell-based therapies as well as increasing manufacturing capability and efficiency to enable a larger scale of cell-based therapeutic production.

R&D Needs

Harmonization and advancement toward these bold goals could be pursued in consultation with the agencies that support research into cell-based therapies (e.g., NIH), support biomanufacturing-capacity

[67] CAR T Cells: Engineering Patients' Immune Cells to Treat Their Cancers | National Cancer Institute

investments (e.g., BARDA), and approve cell-based therapies for clinical use (e.g., FDA) and reimburse patients for their use (e.g., CMS).

To increase therapeutic efficacy **(Goal 3.1)**:

- Develop novel gene-editing techniques and genetic programming that can be leveraged to create next-generation cell-therapies.
- Pair synthetic biology innovations with novel non-viral delivery vehicles, such as lipid or polymeric nanoparticles, to further increase their utility and effectiveness. The fields of synthetic biology and nanotechnology are already working in this space but require further specific effort toward this goal.
- Investigate shipping protocols and storage technologies to keep source and engineered cells at high viability without the use of toxic preservatives, such as dimethyl sulfoxide.
- Develop robust clinical and genomic indicators to identify patients who may be a good candidate for cell-based therapies as well as computational models to identify and predict the therapeutic impact of important engineered qualities of the cell-based therapies.
- Continue support for clinical team science approaches, bringing together clinicians, biologists, engineers, and synthetic biologists.

To increase manufacturing scale **(Goal 3.2)**:

- Identify and develop new source cells that may be more reproducible and less costly than patient cells, such as allogeneic cells or minimal synthetic cells.
- Harmonize methods and standards across cell-based therapy manufacturing facilities by cell types, reducing cost and wait time. The clinical-scale manufacturing of certain cell-based therapeutics is already in place but could benefit from coordination and regulatory insight.
- Develop modular, platform-engineered cell-based technologies alongside patient-specific formulations.
- Provide access to clinical-scale, cell-based manufacturing expertise as a national resource.
- Test and de-risk new biomanufacturing practices for next-generation biotechnology products in commercial-quality manufacturing facilities.
- Partner with clinicians and other hospital staff to create training materials to ensure equity of care across facilities and to consider equipment needs and assignment of clinical staff to patients receiving cell-based therapies.
- Enhance public engagement for the acceptance of cell-based therapies, leveraging experience with existing cell-based therapies such as CAR-T cells.

Theme 4: AI-Driven Bioproduction of Therapeutics

Context for the Bold Goals

While traditional forms of manufacturing therapeutics, such as small molecules, biologics, peptides, and cell-based therapies, can be considered sufficient to meet the demands of patients with common diseases, certain cases require new ways to produce therapeutics quickly and at a large scale, such as occurred during the recent COVID-19 pandemic. New capabilities should be developed to meet the demands of scalability, flexibility, and reliability for the on-demand manufacturing and biomanufacturing of therapeutics. Novel forms of biomanufacturing, such as those involving microbes instead of mammalian cells, have the potential to enable large increases in scale, but a concerted effort is required to identify opportunities to leverage systems of next-generation forms of manufacturing. Artificial intelligence may provide the potential of enabling more distributed manufacturing of therapeutics by optimizing distributed manufacturing and linking physically separated laboratories to act in a cohesive fashion. This potential could be especially useful to respond to large-scale manufacturing needs for biotherapeutics, and this approach could also enable faster design and production of new therapeutics utilizing AI/ML approaches in combination with laboratory automation. The bold goals for achieving this include using automation and AI/ML-enabled therapeutic design and testing techniques to increase manufacturing speed and diversity.

R&D Needs

These efforts could be pursued in consultation with the agencies that support R&D AI/ML methods in biomedicine (e.g., NIH and BARDA) and those that approve biotherapies for clinical use (e.g., FDA).

To increase manufacturing speed: **(Goal 4.1)**:

- Develop a national network of biomanufacturing resources including three core components:
  - A set of distributed, modular, and next-generation autonomous laboratories that focus on capabilities, such as high-throughput screening, sensitive online sensors of relevant metabolites, next-generation sequencing, high-content imaging, polymerase chain reaction diagnostics, and others.
  - A cloud-based virtual research organization to which each distributed automated laboratory is directly connected.
  - A federated model to integrate the physical laboratories with the virtual cloud environment, such that AI methods can be utilized to generate hypotheses based on previous experiments that could then be tested in a physical laboratory environment (i.e., a pre-competitive global lab of experimental data).
- Establish a training program and curriculum for a technical workforce to operate these laboratories.
- Consider biosafety and biosecurity implications.

To increase manufacturing diversity through AI-driven therapeutic design **(Goal 4.2)**:

- Create harmonized and standardized experimental data accessible to researchers anywhere in the country in near real-time to help expedite biotherapeutic development.
- Develop novel AI/ML methods to design therapeutics of every class (e.g., small molecules, biologics, peptides, and cell-based therapies).
- Develop technologies with 10-fold lower limits of detection, accuracy, and precision compared to traditional techniques. In conjunction with quantum computing capabilities, quantum sensors are emerging as technologies for detecting minute amounts of biologics in small samples, enabling analysis of data to diagnose and address complex conditions.
- Develop and operationalize the use of novel technologies for the online sensing of metabolites, physical parameters, and biologics during biomanufacturing.

Theme 5: Advanced Techniques in Gene Editing

Context for the Bold Goals

Millions of Americans every year struggle with diseases caused by genetic mutations, many of which cannot be cured using existing therapies. Recent cures have entered the pharmaceutical marketplace based on gene therapy, including a recent therapy[68] announced that claims to cure beta-thalassemia with only a single injection. Significant progress has been made in the development of gene-editing systems, from novel delivery vehicles, such as viral vectors and lipid nanoparticles, to paradigm-shifting gene editors like CRISPR-Cas9. With further advancement in gene therapy techniques, more cures like these could be applied to other diseases including cystic fibrosis, sickle cell anemia, Tay Sachs, and many rare diseases. Cures can be difficult to develop because of the need for safe and reliable delivery of the gene therapy as well as the financial impracticality of creating specific, complex therapeutics for diseases that affect few patients (in the case of rare diseases). The development of advanced platform technologies to edit problematic genes would immediately enable the development and rollout of therapies toward these diseases. The U.S. can look forward to a future including more cures, but the consistency, reliability, long-term safety profiles, and efficacy of these cures must be addressed through strategic biomanufacturing considerations. The bold goals for achieving this include increasing efficacy of therapeutic gene editors as well as increasing manufacturing capability to meet rising demand.

R&D Needs

These efforts could be pursued in consultation with the agencies that support research into gene therapies (e.g., NIH), work with industry on advanced development and commercialization (e.g., BARDA), and approve gene therapies for clinical use (e.g., FDA) and reimburse patients for their use (e.g., CMS).

To increase efficacy **(Goal 5.1)**:

- Develop gene delivery vehicles, gene editors, and editing systems, building on the success of programs, such as the Somatic Cell Genome Editing program[69].
- Develop standard assays in partnership with the research community (bioengineers; experts in nanotechnology, biomaterials, and synthetic biology; clinicians, and more) to assess editing efficacy *in vitro* and *in vivo* as well as create standard approaches to pair gene editors and delivery vehicles leveraging AI/ML techniques.
- Develop methods to use AI/ML with clinical studies to establish short- and long-term gene editor safety.
- Coordinate stakeholders around unified gene-editing standards through a dedicated stakeholder group composed of expertise in standards development, regulatory considerations (including consultation with FDA), industry and manufacturing capabilities, and academic research.

To increase manufacturing capacity **(Goal 5.2)**:

- Address gaps in the current landscape of contract research organizations (CROs) and contract manufacturing organizations.
  - Create *in chemico, in silico, in vitro,* and *in vivo* core characterization facilities for evaluating the safety and efficacy of gene editors and their delivery vehicles.
  - Engage CROs to assess current capabilities and potentially add new ones.
  - Address clinical infrastructure by installing necessary equipment to receive, store, and prepare gene therapies.

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[68] FDA Approves First Cell-Based Gene Therapy to Treat Adult and Pediatric Patients with Beta-thalassemia Who Require Regular Blood Transfusions | U.S. Food and Drug Administration
[69] Somatic Cell Genome Editing | National Institutes of Health

- Develop gene-editing platform technologies that can be produced at scale and then applied to multiple diseases with little customization.
- Engage the clinical and patient communities to address financial hardship because of the high cost of gene therapies.
- Assess the clinical workflow and pricing for the use of gene therapy.
- Create training materials for clinical staff, patient coordinators, and navigators and assign gene therapy champions at major hospitals to serve as local experts in the application of gene therapy and enable public engagement.

Stakeholder Consultation

These bold goals were identified through a variety of relevant stakeholder workshops and analysis of relevant trends in biotechnology (particularly those funded by NIH) and consideration of feedback from a White House Office of Science and Technology Policy Request for Information and accompanying listening session for the bioeconomy.

Enhancing Biosafety and Biosecurity

Advancement in biotechnology R&D and biomanufacturing drives medical breakthroughs and has made immeasurable positive impacts on American life. Alongside these advancements is a potential risk of laboratory or manufacturing accidents or misuse of medical technologies for harmful purposes, which in turn may cause harm to human health, public trust, or the environment. Such potential risks require the U.S. government, in collaboration with the biomedical community, to continue taking protective actions to appropriately mitigate these risks[70] without placing roadblocks on the discovery and innovation that distinguish the U.S. biomedical enterprise. Implementing appropriate biosafety and biosecurity practices ensures public safety, promotes trust, strengthens integrity in the bioeconomy, and ultimately benefits the public.

The Bioeconomy Executive Order establishes the Biosafety and Biosecurity Innovation Initiative (BBII), charged with reducing biological risks associated with advances in biotechnology, biomanufacturing, and the bioeconomy. BBII will coordinate with key related Administration initiatives, and a forthcoming plan for BBII will outline recommendations for increased Federal investments in several critical areas, including research, workforce development, and culture change. These investments are an important step to enable agencies to adequately manage potential risks throughout the R&D of this report's bold goals.

Existing Biomedical Biosafety and Biosecurity Measures

Federal agencies invest significantly in safety and security throughout the biomedical enterprise. The U.S. has a comprehensive biosafety and biosecurity oversight system driven by Federal regulations, guidelines, and policies. This system is based on identifying and assessing benefits and risks and appropriately mitigating the risks. Also, the U.S. continues to invest in applied biosafety research and biosecurity innovation, training researchers and professionals in biosafety and biosecurity, and infrastructure in support of good biosafety and biosecurity practices. It is critical that, as the biomedical field evolves, we continue to assess and, as needed, update biosafety and biosecurity investments to reduce risk throughout the bioeconomy.

[70] Federal Select Agent Program | Centers for Disease Control and Prevention, U.S. Department of Agriculture; Dual Use Research of Concern | National Institutes of Health; Research Review Under the HHS P3CO Framework | U.S. Department of Health and Human Services

Recommended Actions to Enhance Biosafety and Biosecurity in the Biomedical Enterprise

Using investments proposed through BBII, the following actions will help ensure proper assessment and management of biorisks throughout R&D of the bold goals outlined in this report.

- Assess and manage risks throughout the entire biomedical lifecycle—from conception to product—in a manner that continues to preserve critical discovery and innovation.
- Use evidence-based and iterative approaches to develop metrics that quantify success of biosafety and biosecurity practices and understand where improvement is needed.
- Continue investments in training biomedical professionals, biocontainment and biomedical facility infrastructure, oversight, and applied biosafety research and biosecurity innovation.
- Strengthen the culture of good biosafety and biosecurity practices, in collaboration with government, academia, industry, and the public, that can serve as a model globally.
- Support R&D to enhance cybersecurity and other data protection measures as medical devices and smart manufacturing facilities hold more sensitive information, such as genomic data, disease risk factors, and intellectual property.
- Engage in interagency coordination through BBII to ensure that biosafety and biosecurity information, lessons learned, and good practices are shared by and with the biomedical community.

Opportunities for Public-Private Collaboration

Pursuing opportunities for collaboration across government and in partnership with the domestic and international public and private sectors will be critical to advancing foundational scientific capabilities in biotechnology and biomanufacturing and translating that knowledge into products that improve human health and strengthen the U.S. bioeconomy. A variety of public-private partnerships already exist in the health space; they provide models and lessons learned for future partnerships and could be extended to meet new goals or involve new partners. Such partnerships enable alignment on strategic objectives and coordination of activities across Federal agencies and dozens of stakeholders from academia, philanthropic organizations, and industry to achieve medical breakthroughs.

Existing Public-Private Partnerships

One example is the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL[71]), a public-private partnership (part of Manufacturing USA®) focused on accelerating biopharmaceutical innovation, supporting development of manufacturing standards, and education and training of the biopharmaceutical manufacturing workforce, fundamentally advancing U.S. competitiveness in this industry. Another example is BARDA Ventures, a public-private partnership with private investors using venture capital practices to invest in transformative technologies to advance commercialization of technologies, including in biotechnology and biomanufacturing. The Accelerating Medicines Partnership® (AMP®) program[72] is another example of a public-private partnership between NIH, FDA, the Foundation for the National Institutes of Health, and multiple public and private organizations, including biotechnology and pharmaceutical companies. One project in AMP®, the AMP® Bespoke Gene Therapy Consortium (BGTC),[73] aims to develop platforms and standards that will speed the development and delivery of customized gene therapies.

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[71] National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) | National Institute of Standards and Technology, Manufacturing USA®
[72] Accelerating Medicines Partnership® program | National Institutes of Health
[73] Bespoke Gene Therapy Consortium | National Institutes of Health

Opportunities for U.S. Government Incentivization of Private Sector

Public-private partnerships enable incorporation of industry expertise and promote cooperation between the private sector and the U.S. government. For example, Operation Warp Speed, which transitioned to the Countermeasures Acceleration Group and is now known as H-CORE, and the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)[74] partnership drove important aspects of the Nation's response to the COVID-19 pandemic by accelerating advancements in biotechnology, the conduct of clinical trials, streamlining regulatory pathways, and rapidly sharing data. The AMP® projects have partial funding from the private sector, and private-sector members are partners in governance, stimulating private investment through programs such as the AMP® BGTC. Each of the themes proposed involves significant needs for partners in the private sector, listed in the R&D needs for each theme. The private sector may also benefit from harmonizing safety and quality standards for manufacturing and from the creation of workforce development programs for training to bolster domestic capacity, such as for AI-driven bioproduction of therapeutics **(Theme 4)**.

Opportunities for Public Participation

Several of the themes identified require development of broadly applicable technologies that should be enjoyed equitably by all Americans. Public participation, particularly focused on engagement with diverse populations, will be critical in the development of these tools such that the needs of patient groups as well as clinicians at every level are recognized and considered in the design, manufacture, and application of these technologies. It will be important to seek patient and patient advocate perspectives through public-private partnerships on the awareness and acceptance of novel cell-based therapies to develop implementation strategies that increase equity of access, relevant to **Theme 3**. The same kind of input will be important for all themes, with a special emphasis on the development of advanced gene therapies, multiplexed diagnostic assays, and Health Kits, described in **Themes 5, 2,** and **1**, respectively.

[74] Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) | National Institutes of Health

Biotechnology and Biomanufacturing R&D to Further Cross-Cutting Advances

In collaboration with other U.S. Federal Government departments and agencies, this report was authored by the U.S. National Science Foundation

Executive Summary

We are on the cusp of a biotechnology revolution. Societal problems are increasingly being solved by combinations of fundamental biological discovery and advances in science and engineering fields as disparate as biomaterials and artificial intelligence. New and re-imagined tools like DNA-based diagnostics, whole genome sequencing, and genome editing, which originated through curiosity-driven research, are now commonplace for creating real-world solutions to previously insurmountable challenges in fields from medicine to agriculture to clean energy. For example, COVID-19 tests and mRNA vaccines, developed and deployed within the first year of the SARS-CoV-2 pandemic, saved over 3 million lives. These products of biotechnology would not have been possible without the foundational research that was conducted decades earlier.

To ensure continued rapid advances in biotechnology and biomanufacturing to create the bioeconomy of our future, we must boost innovation along multiple dimensions to protect our climate, improve the health of Americans, support developments in food and agriculture, and build resilient supply chains. This report describes six cross-cutting research and development themes which, if fully funded, would provide the foundational discoveries, innovations, and infrastructure essential to advance all sectors of the bioeconomy.

We must work to **discover and understand the diversity of life (Theme 1)** and how it has adapted to harsh conditions and hard problems. The knowledge gained by tapping into Earth's biodiversity must be coupled with improved capabilities to **predict** the function and behavior of complex biological systems and to use that information for new bio-inspired **design (Theme 2)**. We have tools to automate the **design and manufacture** of biological systems, but they work best for idealized systems like single-celled organisms, not the complex systems of our future needs such as those needed to safely capture rare earth elements by harnessing microbes capable of biomining. In addition, our ability to **measure performance** lags our ability to design and build new systems; we need new measurement tools to accelerate discovery and innovation **(Theme 3)**. **Scale-up** of engineered biological processes from the laboratory to successful commercialization remains dependent on trial and error, and we need new solutions for **understanding and controlling the performance and quality of bioconstructs** in scaled biomanufacturing environments **(Theme 4)**. Existing bioreactor environments barely tap into the potential for **biomanufacturing innovation (Theme 5)**, which is crucially important for accelerating the scope and pace of the bioeconomy revolution. Further, to ensure that new biotechnologies are widely adopted and used by the public, we must **engage end-users early in the ideation and creation (Theme 6)** of such advances.

We highlight bold goals that align with the needs described in the six themes above. Achieving the bold goals within these areas and harnessing the potential power of biotechnology will require investments in basic multidisciplinary R&D, new infrastructure, and public and private collaborations. To fully realize the potential of the U.S. bioeconomy, these investments must be distributed across the nation, expanding the geography of innovation and ensuring equitable access to and benefits from biotechnology and biomanufacturing R&D.

Bold Goals for Harnessing Biotechnology and Biomanufacturing

The following bold goals in cross-cutting R&D are intended to provide a broad vision for the U.S. bioeconomy. These should not be read as commitments by the National Science Foundation (NSF) to undertake specific activities. Achieving these bold goals require significant prioritization of R&D investments and efforts across the U.S. government, as well as actions from the private sector and state, local, and tribal governments.

Theme 1: Leverage Biodiversity Across the Tree of Life to Power the Bioeconomy

Goal 1.1: In 5 years, sequence the genomes of one million microbial species and understand the function of at least 80% of the newly discovered genes.

Goal 1.2: In 20 years, speed discovery of new gene sequences, metabolisms, and functions by 100-fold over current practice across all types of organisms.

Theme 2: Enhance Predictive Modeling and Engineering Design of Biological Systems

Goal 2.1: In 5 years, increase the ability to predictably design small molecules or enzymes capable of binding selectively to any desired target, and reduce the time needed for this process to 3 weeks.

Goal 2.2: In 20 years, leverage multidisciplinary advances in theory to enable high-confidence (90%) design of purposeful engineered biological systems at all scales, from molecular to ecosystem level.

Theme 3: Expand Capabilities to Build and Measure Performance and Quality of Biological Systems

Goal 3.1: In 5 years, develop the capabilities to read and write any genome, epigenome, transcriptome, and expressed proteome to enable the construction and measurement of any single cell within 30 days.

Goal 3.2: In 20 years, build a synthetic minimal plant that can be used as a chassis for food, feedstock, chemical, or pharmaceutical production.

Theme 4: Advance Scale-Up and Control of Biological Systems

Goal 4.1: In 5 years, advance bioprocess design, optimization, and control tools to enable predictable scale-up to commercial production of any bioprocess within 3 months with a 90% success rate.

Goal 4.2: In 20 years, advance integration of all aspects of feedstock use, organism design, process design, and end-of-use disposal with technoeconomic analysis such that sustainability and commercial goals can be achieved for more than 85% of new bioprocesses within the first year of deployment.

Theme 5: Innovate Biomanufacturing Approaches

Goal 5.1: In 5 years, reproducibly manufacture devices that integrate living and non-living components such as organ-chip or human-robotic interfaces that maintain over 90% viability and connectivity of components, paving the way for innovations in biomanufacturing including the development of human-assistive devices that will enable healthier aging.

Theme 6: Enable Ethical, Safe, and Equitable Co-Generation and Translation of Biotechnology Products

Goal 6.1: In 5 years, include broad public and end-user participation; technology co-generation; rigorous assessment; integration of social, behavioral, economic, and socio-technical sciences; and formal evaluations in all biotechnological and biomanufacturing projects from their beginning.

Bold Goals Explored

Theme 1. Leverage Biodiversity Across the Tree of Life to Power the Bioeconomy

Context for the Bold Goals

Unleashing the amazing promise of biotechnology relies on using the diverse capabilities found in living organisms to produce new products and processes with the potential to diagnose and treat disease, develop resilient crops, create clean forms of energy, and more. For example, many of the antibiotics and anticancer drugs we use today were found by exploring the chemicals produced by different microbes and plants. Many enzymes found in laundry detergents came from organisms that live at high temperatures. We are discovering how to make strong glues and even stronger fibers by mimicking processes in barnacles and spiders. We are identifying organisms capable of capturing greenhouse gases and leveraging the power of biotechnology to convert organisms to textiles. These innovations and others like them have sprung out of knowledge of a tiny fraction of the ways that life on Earth has evolved. Imagine what more could be revealed from the estimated millions of species of plants, animals, fungi, and potentially one trillion species of microbes on the planet.

Tapping into this huge reservoir of undiscovered and uncategorized species will provide knowledge of new genes and how those genes create different physical traits, a connection known as genotype-to-phenotype. Moreover, research on all manner of organisms—from microbes to plants to animals—and comparisons among them will be required to identify similarities and differences that can be harnessed in novel biotechnologies and biomanufacturing processes. Achieving the bold goals of sequencing diverse species and learning the functions of their genes will rely on new tools and methods of understanding gene function to accelerate the process and reduce costs. Storing and analyzing huge amounts of genome and phenotype data will require innovations in computing, including artificial intelligence (AI). Using those data to create new products for the bioeconomy will require innovations in bioengineering and biodesign as well as sustained support for needed infrastructure.

R&D Needs

Enhance discovery of novel function from diverse organisms across the tree of life:

- Connect private genome sequencing capabilities with new and existing public capacity to accelerate sequencing output and reduce time and costs.
- Develop a national strategy for selecting organisms to sequence so that comparative analyses are likely to reveal functional variation that can be used for biological design. **(Theme 2)**
- Accelerate development of computational and experimental tools to enhance comparative discovery of sequence and functional elements (e.g., regulatory networks, metabolic pathways, and traits) that define genotype-to-phenotype relationships from evolutionarily diverse organisms and provide the basis for new biotechnology innovations.

Put biodiversity to use in new biotechnology applications:

- Create new and improved technologies to move genes from one organism to another.
- Use outcomes of functional discovery to expand the number of organisms that can be used as hosts (chassis) in engineered biological systems.
- Combine innovations from chemistry and materials science with outcomes of sequencing and functional analyses to expand the repository of “parts” for so-called “plug-and-play” design-build capabilities that incorporate biotic-abiotic interfaces as control elements.
- Create innovation laboratories to leverage learnings from biodiversity studies for bioinspired design of new materials, devices, and products for the bioeconomy.

Enable a robust ecosystem of multiagency, secured data infrastructure for the bioeconomy:

- Collaborate to enhance nationwide capacity for data handling and analysis, including cyberinfrastructure and bioinformatics, to enable equitable, wide-spread access to data from biodiversity studies.
- Align with the open data initiative by encouraging biological data (and biological parts) to be Findable, Accessible, Interoperable, and Reusable (FAIR), and to include standardized metadata and enhance support for cyberinfrastructure and data architectures which permit computation and integration for discovery across diverse datasets. At the same time, balance the need for open data with respect for intellectual property rights to maintain innovation incentives and appropriate data protection and security measures for sensitive data.
- Sustain and enhance living and digitized collections to ensure they remain a resource for diverse downstream applications.
- Support synthesis activities through center-scale investments that enable community-driven use and analysis of data to foster innovations in discovery from across the tree of life.

Theme 2. Enhance Predictive Modeling and Engineering Design of Biological Systems

Context for the Bold Goals

The ability to reliably design biological systems with specified function at all scales has been, and continues to be, a holy grail of engineering biology. Achieving reliable and predictable design would enable creation of drugs from scratch, proteins for enhanced agricultural output, and nature-based climate change mitigation. A key step to rapid progress toward this goal is the use of predictive power to inform and speed the design process.

Great strides in prediction have been made to date by combining fundamental evolutionary and biophysical theory with AI-enabled deep learning. For example, we can now predict the function of a protein from just its genetic sequence. However, this understanding relies on an approach that is only possible on small and simple biological systems. New advances are needed to predict and design biological functions in more complex systems, such as engineered plants that would be more drought tolerant, engineered collections of microbes that could target and capture rare minerals in the soil, or a natural ecosystem more capable of reducing wildfire risks associated with climate change.

Achieving the bold goals for rapid and accurate prediction and design of new biological systems at all scales—from molecules to ecosystems—will require us to incorporate emerging data and new knowledge of biological mechanisms at multiple scales and to leverage new design elements, or parts, gleaned from biodiversity studies **(Theme 1)**. Advances can build on current methods of automation and design that have already been applied to gene circuit construction, and will leverage measurement capacity **(Theme 3)** as well as data from existing ecological observatories. Coupling these advances with learning from iterative prediction and design cycles and the growing power of AI offers unprecedented opportunities to advance engineering of biological systems with desired functions.

R&D Needs

Advance prediction at biomolecular, cellular, organismal, and ecosystem levels:

- Expand the ability to predict the often weak or transient biomolecular interactions that control important functions of small biomolecules and enzymes, including those relevant to drug discovery.
- Leverage advances in signal processing and information theory to predict modes of communication among cells, organisms, and communities for incorporation into biological designs.

- Combine mathematical and computational modeling with knowledge of key steps in development to inform design of artificial tissues and organs or to test human avatars on a dish.
- Use advanced computing and AI to analyze ecosystem data from long-term ecological sites and from continental-scale and ocean observatories to predict ways to design natural systems and mixed human/natural systems that are resilient to the effects of climate change.
- Advance theoretical, computational, and experimental tools at all levels to understand the mechanisms of evolution and adaptation that drive change in biological systems and predict how evolutionary change might be leveraged to positively impact biological design.

Exploit the powers of prediction and AI to advance biological design:

- Develop novel computational algorithms and automation workflows to combine logic and rules enabling prediction of possible constructs with predictive models and libraries of biological parts and their associated functions **(Theme 1)** to enable design of constructable complex cells, organisms, and other complex biological systems.
- Combine AI with knowledge of evolutionary processes to move beyond protein design and accelerate biological design at all scales of biological organization.
- Incorporate knowledge of thermodynamic, biophysical, mechanistic, physiological, and phylogenetic factors to define and constrain the possible design space.
- Develop benchmarking approaches and standards for testing and validating AI-based and other computational models to ensure reliability and trustworthiness of the resulting designs.
- Explore the limits of biological design via both top-down (i.e., breaking down a complex system into component parts) and bottom-up (i.e., piecing together simple parts to make a more complex system) approaches to build cell-free systems, synthetic cells, minimal cell, or organism systems.

Theme 3. Expand Capabilities to Build and Measure Performance and Quality of Biological Systems

Context for the Bold Goals

Moving engineered biological systems from the proverbial drawing board to reality proceeds through the "design-build-test-learn" cycle. Designed systems **(Theme 2)** are built from parts **(Theme 1)** and then tested by measuring their performance. Learning from these tests, powered by AI, completes the cycle by providing information to inform the next generation of design and build steps.

Building and testing new biological systems both face significant hurdles. Building requires specialized technologies for assembling the designed system from component parts so that it functions in the desired fashion. Testing relies on the ability to measure performance of the built system and often takes advantage of components that have been incorporated specifically to report on performance. Of these two steps, testing presents the more substantial bottleneck because the pace at which we can design and build new systems far exceeds our ability to test their performance.

To address these challenges in biological technologies, we need to adopt advances from multiple fields to generate new platforms for manipulating and assembling new systems that not only yield the designed functions but also enable facile testing of performance. Providing broad access to such tools and platforms via public infrastructure will help ensure that we can achieve bold goals. Examples include accelerating the rate of building and testing, or producing engineered whole organisms such as a synthetic plant chassis for food, feedstock, chemical, or pharmaceutical production.

R&D Needs

Expand capabilities for building novel forms and functions:

- Develop advanced technologies for precisely manipulating genomes, transcriptomes, proteomes, and metabolomes of organisms—from microbes to animals and plants—to enable highly predictable spatial and temporal control of complex phenotypes.
- Expand biomaterial design by developing and deploying multi-faceted capabilities, including non-natural biopolymers and their building blocks, chemical functionality across the periodic table, living materials (e.g., abiotic-biotic systems) that can sense and respond to the environment, and biocompatible materials for biomedical components.
- Build platforms for precise high-throughput chemical modification of biomolecules and cells by leveraging knowledge of diverse regulatory pathways and on-off controllers.
- Develop novel modalities for precise assembly of cells into organs, organisms, or ecosystems that incorporate abiotic components as key control or sensing elements.

Expand capabilities for measuring, sensing, actuating, and controlling biological systems:

- Develop biological and non-biological sensors and transducers that do not interfere with cellular function and that take advantage of quantum, optical, magnetic, and other sensing modalities which can receive exogenous signals and interface with biological systems.
- Develop platform technologies to fully read the expressed genome, proteome, and metabolome to enable high-throughput precision phenotyping of any organism.
- Develop platforms and tools for rapid, multimodal measurement of complex signals from cellular and multicellular systems in the context of their interconnected natural and built environments.
- Develop sensor/transducer systems which can both measure and transmit signals that actuate a calculated response, thus enabling open or closed loop control of biological systems. Examples include conversion of undifferentiated cells into mature, functional cells or organoids; assembly of natural or synthetic communities of cells for environmental remediation; and engineering of whole organisms to signal and control a change in nutrient conditions.

Accelerate design-build-test-learn capabilities via public infrastructure:

- Build a national network of biofoundries to enable democratized access to facilities, both virtual and physical, for modern biotechnology associated with design-build-test-learn cycles in cell-free, cellular, organoid, and whole-organism systems.
- Connect biofoundries with expanded publicly accessible repositories of "parts" and sensors.

Theme 4. Advance Scale-Up and Control of Biological Systems

Context for the Bold Goals

Over the past 20 years, the U.S. has been a world leader in biological design and innovation, yet our ability to predictably scale-up and control biological systems has not kept pace. This methodological gap leads to lengthy process development and wasted R&D investment.

A key challenge in the scale-up of biological systems compared to more traditional industries such as petrochemicals is that, unlike chemicals, biological systems behave differently depending upon the environment. For example, a cell engineered to produce a commodity chemical might deliver high yields when grown in the lab in a 100-milliliter flask, but that performance can change dramatically when scaled up to a commercial scale of 10,000 liters. Another complication in commercial-scale production is that organisms are frequently designed to produce a biochemical without considering how the chemical will be purified after production or be disposed of at the end of its use. This lack of integration at the outset leads to high costs and unneeded waste, impeding successful commercialization. Thus, to achieve bold goals of speeding scale-up for simple bioprocesses as well as integrated industrial-scale operations, a compelling need exists to integrate new developments in predictive modeling of biological processes **(Theme 2)** and measurement **(Theme 3)** with advances in process engineering to advance the science of scale-up and control of biological systems.

R&D Needs

Accelerate scale-up via robust process modeling, optimization, and design:

- Develop the ability to predict performance and behavior (including evolution) of cells, organisms, systems of organisms, and the molecules they use and produce in complex production and processing environments.
- Advance theory-driven and AI-enabled multiscale modeling using data from biofoundries to couple models of biological system performance with models of bioprocess performance.
- Integrate optimization parameters across all aspects of the bioprocess, including design, upstream and downstream processes, product end-of-life, and non-conventional bioprocess environments.
- Improve bioproduct supply chain resiliency by advancing process design methods to transition from (semi)-batch to continuous and intensified processes, including through the use of modular, geographically distributed, and potentially reconfigurable processes or facilities.
- Advance capabilities in digital twins across a broad range of application spaces, including both in-fermenter and outside the fermenter applications.
- Leverage existing Manufacturing USA institutes and other public and private infrastructure to support model validation via prototypes and scaled-up or scaled-down systems.
- Develop robust tools for technoeconomic analysis and life cycle assessment that can be integrated within the design process.

Advance biological process control:

- Advance the capacity to develop process control strategies that include control at the cellular level (e.g., embedded sensors/actuators within cells, **Theme 3**) and at the whole-system level.
- Advance model-based process optimization and control that can explicitly account for biological uncertainty, stochasticity, and variation in biological as well as physical systems.
- Advance estimation techniques to predict the many states (e.g., cell phenotype, protein expression, or enzyme activity) of biomanufacturing processes that cannot be measured directly.

Theme 5. Innovate Biomanufacturing Approaches

Context for the Bold Goals

New biotechnologies and bio-inspired designs hold the potential to extend human capability, increase health, and enable forms of data storage and computation requiring far less space and energy than conventional systems. However, to realize these and other potential applications, new forms of biomanufacturing are required.

Innovations in biomanufacturing modalities will need to leverage all the advances in R&D envisioned in **Themes 1 through 4**, together with advances in multi-materials processing, robotics, and cyber-manufacturing. To achieve the bold goal of producing devices that integrate living and non-living components and pave the way for assistive devices to benefit human health, advances will be needed in sensors, the internet of things, autonomy, human-machine teaming, and computation at the human-technology frontier. Moreover, new methods and processes are necessary to develop new application-specific uses (e.g., human-machine interfaces, wearable devices, and biotechnologies that augment human capabilities) and provide alternative fuels and infrastructure materials. Again, realizing new methods and processes proceeds through the "design-build-test-learn" cycle.

R&D Needs

Innovate in biomaterials manufacturing:

- Advance capabilities in nanomanufacturing that leverage biobased nanomachines and designs.
- Develop engineered biological and biomanufacturing systems to produce biopolymers and process them *in situ* and at scale, thereby enabling manufacture of biomaterials which mimic those found in nature such as insect silks or exoskeletons.

Advance integration of cells and tissues with devices and the creation of multi-materials:

- Advance development of bio-enabled processes using DNA, viruses, and bacteria, including DNA-enabled self-assembly for data storage applications.
- Advance capabilities for bioprinting cell scaffolds, bone or cartilage replacements, and multi-material structures to mimic or replace living tissues. Advance capabilities for bioprinting in applications including fuels, electronics, and materials.
- Incorporate the potential for new cells and tissues to participate in sensing, actuating, data capture, feedback, repair, and scale-up of manufacturing printed living materials reproducibly.
- Advance capabilities for manufacturing functional neuron or brain organoid devices, both for neuronal stimulation and repair and for potential biological computing applications.

Create innovations at the human-technology frontier:

- Develop manufacturing of wearable and ubiquitous technology to provide enhanced mobility and assist with communication and everyday needs.
- Create appropriate technologies to improve worker productivity and quality of life, including collaborative physical and cognitive assistance, seamless augmented reality and telepresence, and private and secure health and wellness monitoring.

Theme 6. Enable Ethical, Safe, and Equitable Co-Generation and Translation of Biotechnology Products

Context for the Bold Goals

New discoveries from across the tree of life **(Theme 1)**, advancements throughout the design-build-test-learn cycle **(Themes 2 and 3)**, new scale-up capabilities **(Theme 4)**, and innovative biomanufacturing approaches **(Theme 5)** will provide a wealth of foundational, technical, and practical know-how for advancing biotechnology and biomanufacturing. However, the promise of these advances to positively impact the bioeconomy will depend largely on public willingness to adopt and use these new innovations. This cannot be taken for granted. For example, recent research suggests many people and nations still doubt the safety of genetically modified foods. To help ensure that the biotechnology advances proposed in this report will be embraced, we must engage stakeholders and end users early and often as the technology is designed, implemented, and deployed.

Achieving the bold goal of involving the public from the outset will require evidence-based, collaborative new approaches and methods of engagement, changes in practice, and coordination across the product lifecycle from discovery through design and disposal. We also will need to develop the evidentiary basis of the science of science, social and behavioral research, and economics. This will ensure use of rigorous, data-driven approaches to inform best practices enabling ethical, safe, and equitable translation of biotechnology products.

R&D Needs

Develop biotechnology foci within the social sciences:

- Develop new research opportunities within the social sciences with a focus on biotechnology and biomanufacturing.
- Advance the science of public engagement and public participation, as applied to biotechnology and biomanufacturing, to develop an evidentiary basis for meaningful public involvement in considerations of biotechnology.
- Invest in programs and efforts that incorporate social scientists within research teams working in fields related to biotechnology and biomanufacturing.
- Conduct research on ethical issues related to biotechnology and biomanufacturing to develop new understanding of how ethical concerns can inform public policies around biotechnology and biomanufacturing.
- Develop new methods and processes to incorporate ethical, societal, decision-making, and economic research into decisions at all phases of biotechnology development.

Enhance the evidentiary basis to ensure the safety of products and processes of the bioeconomy:

- Develop the capability to assess the health and environmental risks of products and processes of the bioeconomy.
- Expand investments in research to enable science-based regulation of products and processes.

Enhance diversity and equity within biotechnology and biomanufacturing R&D:

- Expand investments in equity-focused science, including social justice, environmental justice, and equity-advancing efforts, such as the Analytics for Equity Initiative led by NSF in partnership with the Office of Science and Technology Policy (OSTP) and other research-backed efforts, to advance better, more equitable outcomes for all of America.
- Develop educational and training pathways to broaden participation of underrepresented groups to ensure diverse perspectives are included in future biotechnology and biomanufacturing R&D.
- Expand investments in accessibility to enable all individuals to participate in the bioeconomy and benefit from biotechnology and the bioeconomy regardless of disability.

Stakeholder Consultation

This report was informed by community input gathered from a recent workshop series on Innovation in the Bioeconomy, sponsored by NSF and facilitated by the University Industry Demonstration Partnership. Valuable perspectives were also provided by policy papers from the Engineering Biology Research Consortium (EBRC) and the Engineering Research Visioning Alliance, as well as input via OSTP-sponsored listening sessions and a Request for Information from the National Biotechnology and Manufacturing Initiative.

Enhancing Biosafety and Biosecurity

Foundational R&D in biotechnology and biomanufacturing can create immense benefits in fields such as agriculture, medicine, energy, and climate science. It can also raise questions and highlight gaps related to safety and security, both in the R&D process and in resulting products. Alleviating these concerns requires public-private collaboration, community engagement, and development of best practices that can be applied across sectors to ensure safety, enhance security, and promote trust.

Current concerns in biosafety and biosecurity associated with foundational R&D and the cross-cutting advances meant to enable the whole bioeconomy include a lack of critical infrastructure in the U.S. and vulnerabilities within existing infrastructure; lack of scientific, technological, and engineering expertise within the American biotechnology and biomanufacturing workforce; and potential for accidental or purposeful creation and/or release of organisms or systems that could harm the environment or the public.

Lack of infrastructure, including sequencing and synthesis capabilities, open data repositories and computational capabilities, biological parts collections, and biofoundries, creates the potential for stalled development and offshoring of R&D to the detriment of the U.S. bioeconomy. Similarly, a lack of needed expertise within the workforce, detailed in a separate report, increases the possibility of critical technologies not making it to market.

Existing infrastructure requires increased investment to alleviate concerns around cybersecurity attacks, introduction of contaminants into the supply chain, and physical breakdown of or attack on critical repositories or parts of the supply chain. Such incidents could be purposeful or malicious, but they may also result from accidents or aging systems; either cause can result in potential harm to the environment or the public.

Mitigating the risks of accidental or purposeful design or release of harmful organisms requires an expanded evidentiary basis to enable the prediction of biosafety risks of any synthetic sequence, part, or organism. Technological innovations at sequencing, foundry, and scale-up facilities are also needed to prevent accidental manufacture and release of potentially harmful agents.

Recommended New Biosafety and Biosecurity Measures

The Bioeconomy Executive Order calls for creation of a government-wide Biosafety and Biosecurity Innovation Initiative (BBII) to enhance biosafety and biosecurity across the bioeconomy while maximizing its benefits. In alignment with BBII plan recommendations, reducing biorisks associated with foundational R&D, which cut across all sectors, will require support for critical infrastructure, workforce development, cybersecurity as described above, and enhanced R&D on biocontainment, organismal digital identifiers, and sequences of concern.

Opportunities for Public-Private Collaboration

Public-private partnerships represent a key component of the investments necessary to spur advances across all sectors of the bioeconomy. These collaborations, both domestic and international, will enable and support the necessary physical and cyberinfrastructure required to conduct fundamental R&D, ensure connections between researchers and end-users, and translate new discoveries to the market at speed and scale. They also provide an opportunity to advance equity and broaden participation through intentional efforts to ensure involvement of underrepresented racial and ethnic groups and communities.

Existing Public-Private Partnerships

Existing public-private partnerships include industry-academia consortia such as EBRC, Manufacturing USA institutes, and efforts connecting academia with industry. Leveraging these extant connections will enable development of critical pipelines from academia through small business to industry at scale **(Themes 1-5)**, support crucial engagement of stakeholders **(Theme 6)**, and inform policy development with respect to biosecurity and biosafety risks.

Opportunities for U.S. Government Incentivization of Private Sector

Additional public-private interfaces can build consensus for strategic sequencing and data for bioeconomy initiatives and consolidate efforts to maximize bioeconomy impacts. Sequencing capabilities developed during the SARS-CoV-2 pandemic can be leveraged to address data for bioeconomy needs. Leveraging existing biofoundries and pilot or production capacity, as well as repurposing existing infrastructure, provides government-supported small businesses and researchers with low-cost or subsidized access to critical design-build-test-learn capabilities needed to develop new biotechnologies **(Themes 2 and 3)** or advance biomanufacturing **(Theme 5)**, and access to needed scale-up infrastructure **(Theme 4)**. Partnerships with companies with sizeable computing power will help build the data fabric and systems needed to support the large amounts of existing and to-be-created biological data from large-scale biodiversity studies **(Theme 1)**.

Opportunities for Public Participation

In addition to engaging with the public sector in the partnerships and connections outlined above, the private sector can provide in-kind support for any of the R&D needs listed in this report; collaborate with academia on development of critical technology, tools, and infrastructure; provide novel educational and internship opportunities to enhance the future workforce; and collaborate with foundations in such efforts.

Public engagement and participation are critical to the success of biotechnology and biomanufacturing efforts **(Theme 6)**. Pilot programs can identify best practices in community engagement and knowledge co-generation as research on the science of science advances. These practices can increase interest in biotechnology and biomanufacturing among diverse individuals across education levels.

Building on the successes of crowdfunding in the private sector, the U.S. government could invest in pilot projects to facilitate crowdfunding of translational activity. The public could also engage through citizen science programs. Similarly, research can benefit from public interest such as through efforts to leverage idle computational capacity like Folding@Home, which utilizes volunteered computing power to run protein folding simulations that have assisted in developing therapeutics to fight disease.

Appendix A. Agency Research and Development Efforts

Ongoing R&D activities from Federal departments and agencies related to bold goal themes are listed in the table below.

Section (Lead Agency)	Theme	DOE	USDA	DOC	HHS	NSF	DOD	EPA	NASA
Climate Change Solutions (DOE)	Expand Transportation and Stationary Fuels	●	●	●		●	●		●
	Develop Chemicals and Materials	●	●	●		●	●		●
	Develop Climate-Focused Agricultural Systems and Plants	●	●	●		●			●
	Accelerate Carbon Dioxide Removal	●	●	●		●	●		●
Food and Agriculture Innovation (USDA)	Improve Sustainability and Resource Conservation While Increasing Agricultural Productivity	●	●	●		●	●		●
	Increase Food Nutrition, Quality, and Consumer Choice	●	●	●	●		●		●
	Protect Plants and Animals Against Biotic and Abiotic Stressors	●	●	●		●		●	●
Supply Chain Resilience (DOC)	Promote Economic Security Through Alternative Supply Chain Pathways via Biotechnologies and Biomanufacturing	●	●	●	●	●	●		●
	Enhance Supply Chain Resilience Through Biomanufacturing Innovation	●	●	●	●	●	●		●
	Develop Standards and Data Infrastructure to Support Biotechnology and Biomanufacturing Commercialization and Trade	●	●	●	●	●	●		●
Human Health (HHS)	Provide Accessible Health Monitoring			●	●	●	●		●
	Develop Precision Multi-Omic Medicine	●		●	●	●	●		●
	Advance Biomanufacturing of Cell-Based Therapies			●	●	●	●		●
	Use AI to Drive Bioproduction of Therapeutics	●		●	●	●	●		
	Develop Advanced Techniques for Gene Editing			●	●		●		
Cross-Cutting Advances (NSF)	Leverage Biodiversity Across the Tree of Life to Power the Bioeconomy	●	●	●	●	●	●		●
	Enhance Predictive Modeling and Engineering Design of Biological Systems	●	●	●	●	●	●	●	
	Expand Capabilities to Build and Measure Performance and Quality of Biological Systems	●	●	●	●	●	●		
	Advance Scale-Up and Control of Biological Systems	●	●	●	●	●	●		
	Innovate Biomanufacturing Approaches	●		●	●	●	●		
	Enable Ethical, Safe, and Equitable Co-Generation and Translation of Biotechnology Products	●	●	●	●	●	●	●	●