# Project BOoST: a biomanufacturing test facility network for Bioprocess Optimization, Scaling, and Training

## Summary

The U.S. bioeconomy commands millions of liters of bioproduction capacity, but only a tiny fraction of this capacity supports process optimization. Companies of all sizes face great pressures that limit their ability to commit resources to these important efforts. Consequently, the biomanufacturing industry is often forced to juggle sensitive, brittle production processes that don't scale easily and are prone to disruption. As some recent failures of prominent companies demonstrate, this increases risk for the entire bioeconomy, and especially for the development of new companies and products.

To remedy this, the Department of Commerce should first allocate $80 million to seed a bioproduction R&D facility network that provides process optimization capability to the greater bioeconomy, followed by a $30 million process optimization challenge wherein participating facilities compete at workflow optimization, scaling, and transfer. Part one of the proposal requires rapid development, with the initial R&D facility network of four sites starting bioprocessing operations within 12 months of award. In addition to training workers for the greater bioeconomy, the facility network's services would be available on a contract basis to any company at any stage of maturity. This work could include optimization for yield, scaling, process resilience, and/or technology transfer—all critical needs across the sector. After federal government startup funding, the network would transition toward financial independence, increasingly running on revenue from process optimization work, workforce training, and state/local support.

Part two of the plan lays out a biomanufacturing "Grand Challenge" in which participating network facilities compete to optimize a standardized biomanufacturing process. Prioritizing process resilience, security, and transferability in addition to yield, this effort would help set a new industry standard for what process optimization really means in addition to demonstrating what can be accomplished by the network facilities. With this demonstration of value, demand for facility services in other geographic locations would increase, spurring the growth of the facility network across the country.

By the end of the program, the U.S. biomanufacturing sector would see a number of benefits, including easier process innovation, a larger and better trained workforce, shortened product time to market, and reduced production risks.

## Challenge & Opportunity

Biological products are, by definition, made by means of complex biological processes carried out by sensitive—some might even say fickle—microorganisms and cell lines. Determining the right steps and conditions to induce a microbe into producing a given product at a worthwhile

yield is an arduous task. And once produced, the product needs to be extensively processed to make it pure, stable, and safe enough for shipping and use. Working out this entire production workflow takes a great deal of time, energy, and expertise, and the complexity of production workflows increases alongside the complexity of biological products. Many products fail at this point in development, keeping beneficial products out of the hands of end users and cutting off constructive contributions—revenue, jobs—to the larger bioeconomy.

Once a bioproduction process is worked out at an R&D level, it must be scaled up to a much larger commercial level—another major point of failure for academic and commercial programs. Scaling up requires different equipment with its own controls and idiosyncrasies, each generating additional, sometimes unpredictable, complexities that must be corrected for or managed. The biomanufacturing industry has been asking for help with process scaling for years, and recent national initiatives, such as the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) and the BioIndustrial Manufacturing and Design Ecosystem (BioMADE), have sought to address this strategic need.

Each step on this road to the end market represents a chance for failure, and the risks are so high that the road is littered with failed companies that had a promising product that just couldn't be made reliably or a brittle production process that blew up when performed at scale. The overarching competitive commercial environment doesn't help, as new companies must rush from concept to production, often cutting corners along the way. Meanwhile, mature biomanufacturing companies often nurse small profit margins and must aggressively guard existing revenue streams, leaving little or no spare capacity to innovate and improve processes. All of these factors result in production workflows that are hastily constructed, poorly optimized, prone to scaling difficulties, and vulnerable to failure at multiple points. When—not if—process failures occur, the entire economy suffers, often in catastrophic ways. In the last several years alone, such failures have been witnessed at Emergent Biosciences, Dr Reddy's, and Abbott, with any number of downstream effects. Society, too, misses out when more sustainable, environmentally friendly production methods are overlooked in favor of older, less efficient but more familiar ones.

There is an urgent need for a national network of biomanufacturing facilities dedicated to process optimization and scaling—critical efforts that are too often overlooked or hastily glossed over, to the subsequent detriment of the entire bioeconomy. Available to any company at any stage of maturity, this facility network would operate on a contract basis to optimize biological production processes for stability, resilience, and technology transfer. The facilities would also assist with yield optimization, in addition to incorporating the specialized equipment designed to aid in scale-up risk analysis. Once established with government funding, the facility network would stand on its own, running on contract fees for process optimization and scale-up efforts. As demand for services grows, the facility network model could spread out geographically to support other markets.

This a highly opportune time for such a program. The COVID-19 pandemic has highlighted the essential importance of biomanufacturing capabilities—extending to the geopolitical level—as well as the fragility of many supply chains and processes. In response, the CHIPS and Science Act and Executive Order on Advancing Biotechnology and Biomanufacturing, among others, have provided directives to shore up U.S. biomanufacturing

capacity and resilience. Project BOoST seeks to meet those directives all while building a workforce to support broader participation in a strong national bioeconomy.

## Plan of Action

Project BOoST encompasses a $110 million ask spread out over four years and two overlapping phases: a first phase that quickly stands up a four-facility network to perform biomanufacturing process optimization, and a second phase that establishes a biomanufacturing "Grand Challenge" wherein facilities compete in the optimization of a standardized bioproduction process.

### Phase I: Establishing the facility network

The Department of Commerce should allocate $80 million over three years to establish the initial facility network at four sites in different regions of the country. The program would be structured as a competitive contract, with a preference for contract bidders who:

- Bring along industry and academic partners, as evidenced by MOUs or letters of support
- Have industry process optimization projects queued and ready to commence
- Integrate strong workforce development initiatives into their proposals
- Include an entrepreneurship support plan to help startups advance through manufacturing readiness levels
- Leverage state and local matching funds and have a plan to grow state and local cost-share over time
- Prioritize process resilience (including supply chain) as much as yield optimization
- Prioritize data and process security, both in terms of intellectual property protection and cyber protection
- Propose robust means to facilitate process transfer, including developing data standards around process monitoring/measurement and the transfer process itself
- Have active means of promoting economic, environmental, social, and other forms of equity

Possible funding pathways include one of the bio-related Manufacturing Innovation Institutes (MIIs), such as NIIMBL, BioMADE, or BioFabUSA. At a minimum, partnerships would be established with these MIIs to disseminate helpful information gained from the facility network. The National Institute of Standards and Technology (NIST) could also be helpful in establishing data standards for technology transfer. The Bioeconomy Information Sharing and Analysis Center (BIO-ISAC) would be another important partner organization, helping to inform the facilities' efforts to increase both cyber resilience of workflows and industry information sharing.

Funds would be earmarked for initial startup expenditures, including lease/purchase of appropriate buildings, equipment purchases, and initial salaries/benefits of operating personnel, trainers, and program support. Funding milestones would be configured to encourage rapid movement, including:

- 6-month milestone for start of workforce training programs
- 12-month milestone for start of bioprocess operations
- 12-month milestone for training program graduates obtaining industry jobs

Since no actual product made in these facilities would be directed toward regulated use (e.g., food, medical), there would likely be reduced need to build and operate the facilities at full Current Good Manufacturing Practice (CGMP) specification, allowing for significant time and cost savings. Of course, the ultimate intent is for optimized and scaled production processes to migrate back to regulated use where relevant, but process optimization need not be done in the same environment. Regardless, the facilities would be instrumented so as to facilitate bidirectional technology transfer. With detailed telemetry of processes and data traffic collected in a standardized manner from the network's sites, organizations would have a much easier time bringing optimized, scaled processes from these facilities out to commercial production. This would result in faster parameter optimization, improved scale-up, increased workflow resilience, better product assurance, and streamlined tech transfer—all of which are major impediments and risks to growth of the U.S. bioeconomy.

Process optimization and scaling work would be accomplished on a contract basis with industry clients, with robust intellectual property protections in place to guard trade secrets. At the same time, anonymized information and techniques gathered from optimization and scaling efforts would be automatically shared with other sites in the network, enabling more globalized learning and more rapid method development. These lessons learned would also be organized and published to the relevant industry organizations, allowing these efforts to lift all ships across the bioeconomy. In this way, even a facility that failed to achieve sufficient economic self-sustainability would still make significant contributions to the industry knowledge base.

Focused on execution speed, each facility would be a public-private consortium, bringing together regional companies, universities, state and local governments, and others to create a locus of education, technology development, and job creation. In addition to hewing to provisions within the CHIPS and Science Act, this facility network would also match the "biomanufacturing infrastructure hubs" recommendation from the President's Council of Advisors on Science and Technology.

Using the Regional Technology and Innovation Hubs model laid out in the CHIPS and Science Act, the facilities would be located near to, but not within, leading biotechnology centers, with an eye to benefiting small and rural communities where possible. All the aforementioned stakeholders would have a say in site location, with location criteria including:

- Level of partnership with state and local governments
- Degree of involvement of local educational institutions
- Proximity to biomanufacturing industry
- Positive impact on economic/environmental/social equity of small and/or rural communities
- Availability of trainable workforce

Although some MIIs have innovation acceleration and/or improving production availability within their charters, to date no production capacity has been built specifically to address the critical issues of process optimization and scaling. Project BOoST would complement the

ongoing work of the bio-focused MIIs. And since the aforementioned risks to the bioeconomy represent a strategic threat today, this execution plan is intentionally designed to move rapidly. Locating network facilities outside of costly metropolitan areas and not needing full cGMP certification means that an individual facility could be spun up in months as opposed to years and at much lower cost. These facilities would quickly be able to offer their benefits to industry, local economies, and workers looking to train into a growing job sector.

## Phase II: Scale-up challenge

Approximately 30 months from program start, facilities that meet the aforementioned funding milestones and demonstrate continuous movement toward financial self-sustainability (as measured by a shift from federal to state, local, and industry support) would be eligible to participate in an additional $30 million, 18-month scale-up challenge, wherein they would receive a reference production workflow so they could compete at workflow optimization, scaling, and transfer.

In contrast to previous Grand Challenges, which typically have a unifying theme (e.g., cancer, clean energy) but relatively open goals and means, Project BOoST would be hyperfocused to ensure a high degree of applicability and benefit to the biomanufacturing industry. The starting reference production workflow would be provided at lab scale, with specifications of materials, processing steps, and instrument settings. From this starting point, participating facilities would be asked to characterize and optimize the starting workflow to produce maximal yield across a broad range of conditions; scale the workflow to a 1,000L batch level, again maximizing yield; and transfer the workflows at both scales to a competing facility both for verification purposes and for proof of transferability.

In addition, all competing workflows would be subject to red-teaming by an independent group of biomanufacturing and cybersecurity experts. This examination would serve as an important assessment of workflow resilience in the setting of equipment failure, supply chain issues, cyberattack, and other scenarios.

The winning facilities—represented by their workflows—would be determined by a combination of factors:

- Maximum yield
- Process transferability
- Resistance to external tampering
- Resilience in the setting of equipment/process/supply chain failure

The end result would be the practical demonstration and independent verification of the successful optimization, scale-up, and transfer of a production process—a major opportunity for learning and knowledge sharing across the entire industry.

# Conclusion

Scientific innovation and advanced automation in biomanufacturing represent a potent double-edged sword. While they have allowed for incredible advances in biomanufacturing capability and capacity—to the benefit of all—they have also created complexities and dependencies that together constitute a strategic risk to the bioeconomy. This risk is a significant threat, with process failures already creating national headlines out of company collapses and congressional investigations. We propose to act now to create a biomanufacturing facility network dedicated to making production workflows more robust, resilient, and scalable, with a plan strongly biased toward rapid execution. Bringing together commercial entities, educational institutions, and multiple levels of government, Project BOoST will quickly create jobs, provide workforce development opportunities, and strengthen the bioeconomy as a whole.

## FAQs

1) What differentiates Project BOoST from other facilities and networks proposed by MIIs, current Centers for Innovation in Advanced Development and Manufacturing (CIADMs), and the Department of Defense (DoD) authorization to support bioindustrial R&D included in the National Defense Authorization Act?

| | Project BOoST | MIIs | CIADMs | DoD/NDAA |
|---|---|---|---|---|
| Time frame to start of facility operations | Estimated 12 months from funding | Unknown—as of yet no new ground broken | Already operational, although only one surviving | Unknown—plan to meet goals of act due 6/2023 |
| Geographic location | Targeting small and rural communities | Unknown | Mix: urban and less urban | Unknown |
| Scope | Process optimization, resilience, and scaling, including scale-up risk assessment | DOD MII: TRL acceleration in nonmedical products<br>DOC MII: accelerate biopharmaceutical innovation | Maintenance of critical product stockpiles, reserve production capacity | Research into new methods, capacity building, scaling |
| Financial model | Initial government funding with transition to self-sufficiency | Government funding plus partner contributions | Persistent government funding | Unknown |

2) Will this effort address supply chain threats?

Yes. Supply chain resilience will be a constant evaluation criterion through the program. A more resilient workflow in this context might include onshoring and/or dual sourcing of critical reagent supplies, establishing on-site reserves of single-point-of-failure equipment, maintaining backups of important digital resources (e.g., software, firmware, ladder logic), and explicitly rehearsing failure recovery procedures.

3) What kind of workforce training opportunities would be available at these facilities?

While the specifics will be left up to the contract bidders, we recommend training programs ranging from short, focused trainings for people already in the biomanufacturing industry to longer certificate programs that can give a trainee the basic suite of skills needed to function in a skilled biomanufacturing role.

4) Why can't industry address these issues on its own?

They would if they could. On a fundamental level, due to the nature of the U.S. economic system, the biomanufacturing industry is focused on competition, and there's a lot of it. Industry organizations, whether large or small, must be primarily concerned with some combination of generating new products and producing those products. They are unable to devote resources toward more strategic efforts like resilience, data standards, and process assurance simply because energy and dollars spent there means less to put toward new product development or increasing production capacity. (Contrast this to a country like China, where the government can more easily direct industry efforts in a certain direction.) Revolutionary change and progress in U.S. biomanufacturing requires the public sector to step up to solve some of these holistic, longer-term challenges.

## About the Authors

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Ed Chung, MD, is COO of Black Mesa. He has degrees in biology and chemical engineering from MIT and an MD from the Duke University School of Medicine. His career path has taken him through roles in clinical leadership, the healthcare C-suite, and the startup space, working to build new product and service lines, fight worker burnout, and bring data to bear in both medicine and biology. In addition to his work at Black Mesa, Dr. Chung remains active as a pediatric hospitalist and is also a medical officer for the MA-1 Disaster Medical Assistance Team. He continues to work to improve people's health and well-being at both the individual and macro levels.