NIIMBL® The National Institute for Innovation in Manufacturing Biopharmaceuticals

ANNUAL REPORT

2022 2023

START →

This Annual Report covers accomplishments and activities from March 1, 2022 to June 30, 2023.

mission

The NIIMBL mission is to accelerate biopharmaceutical manufacturing innovation, support the development of standards that enable more efficient and rapid manufacturing capabilities, and educate and train a world-leading biopharmaceutical manufacturing workforce, fundamentally advancing U.S. competitiveness in this industry.

vision

NIIMBL will lead and transform the development and adoption of next-generation biopharmaceutical manufacturing technologies that contribute to patient well-being. As a public–private partnership, NIIMBL will forge and catalyze advancements that are vital to the acceleration of innovative technologies and a skilled workforce, and these strategic efforts and investments will be undertaken to secure U.S. biopharmaceutical manufacturing leadership.

ACCOMPLISHMENTS

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A Letter to the Community

Progressing and Growing Together

Dear Colleagues,

We are pleased to present our 2022-2023 Annual Report. Through projects, NIIMBL-led Programs, and talent initiatives, our community continues to seize opportunities to drive innovations that will enhance patient access to medicines, strengthen our economy, and boost national security.

In 2022-2023, we invested $11M in new technology projects in areas such as mRNA vaccines, cell processing, critical quality attribute measurement, and reliability. We also invested $2.5M in workforce development projects to increase awareness of our industry and foster alternative education pathways for careers in the biopharmaceutical industry.

Our NIIMBL-led Programs have matured and gained considerable momentum over the past year. We outfitted our lab space at NIIMBL headquarters with new equipment, allowing our industry members to collaborate and test new processes. And the continued progress in our American Rescue Plan projects is poised to help our nation prevent, prepare for, and respond to future health threats.

As part of our commitment to increasing diversity within our industry, we expanded our well-received NIIMBL eXperience program to three new locations across the country. This approach offered 3x more students the opportunity to explore a variety of career paths in biopharmaceutical manufacturing.

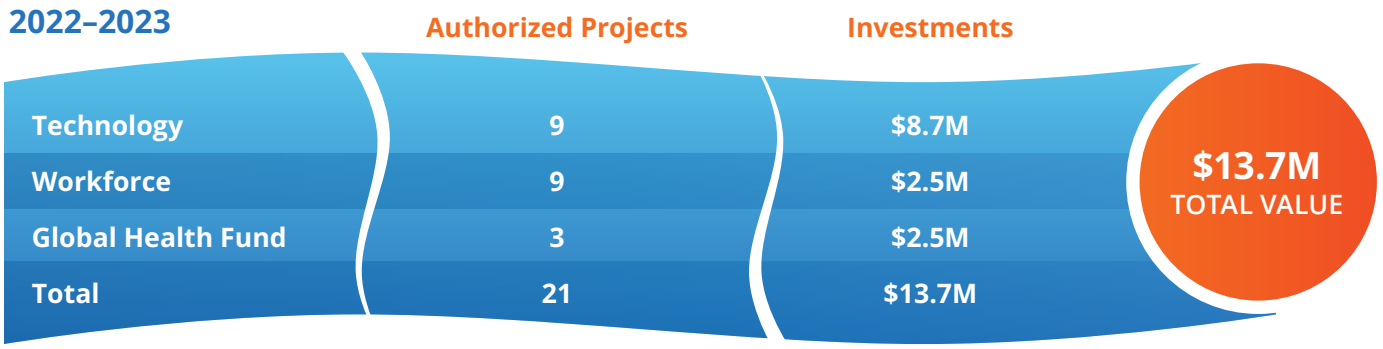
While we celebrate the success of the past year, we are even more thrilled to look toward the future. The progress our institute has made in just six years is a testament to the dedication and enthusiasm of our members and community. We thank you for your continued commitment and look forward to collaborating on more advances in the years to come.

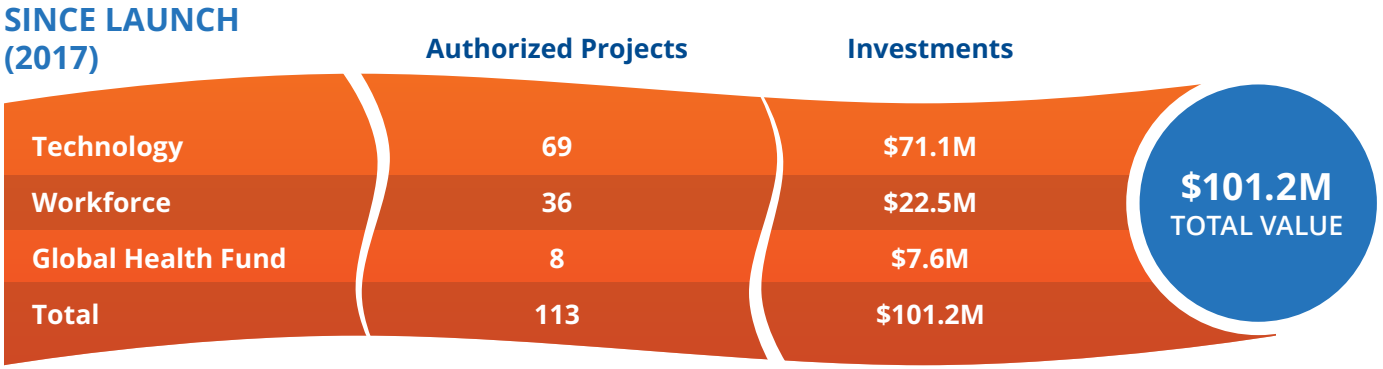
Sincerely,

The NIIMBL Team

Member-led Project Investments

121 Collaborating Organizations





American Rescue Plan

32 Projects

Workforce Development

Strengthening the biopharma talent pipeline

With advancing technologies, emerging treatment modalities, and expanding product portfolios, the biopharmaceutical industry faces an increased need for talent to fill critical manufacturing roles. Our workforce development initiatives help industry close these skills gaps and expand the pipeline of qualified workers. Our workforce development initiatives include:

- Developing new education programs for students, career changers, and experienced professionals.
- Introducing students to careers in biopharmaceutical manufacturing.
- Promoting novel "skills-first" pathways into the industry, including apprenticeships, certification programs, credentialing initiatives, and micro-credentials.
- Fostering industry and academic connections to facilitate additional sources of talent.
- Connecting students and early-career talent to open positions, internships, and educational opportunities.
- Encouraging diversity and inclusion in the biopharmaceutical industry.

In 2022, NIIMBL workforce programs and initiatives reached

4,000 PROFESSIONALS

2,000 STUDENTS

Workforce Development

NIIMBL eXperience

Our successful NIIMBL eXperience program continued to grow in 2022-2023, reaching more students than ever before. Launched in 2019, the NIIMBL eXperience is a week-long immersive program designed to introduce Black, Latine, and Indigenous college students to biopharmaceutical industry careers. The program is part of NIIMBL's efforts to expand diversity in the industry.

2022 NIIMBL eXperience

In June 2022, the NIIMBL eXperience returned as an in-person program for the first time since 2019. Students took part in a personal branding workshop led by the National Society of Black Engineers. In addition, the students visited local host organizations for facility tours and hands-on activities. Hosts included AstraZeneca, Cytiva, GlaxoSmithKline, Jefferson Institute for Bioprocessing, Merck & Co., Inc., MilliporeSigma, Montgomery County Community College, the National Institute of Standards and Technology, and Pfizer. After a packed week, students took away a deeper understanding of the industry and the career paths it offers.

NIIMBL eXperience @ACPHS

Led by Albany College of Pharmacy and Health Sciences in New York

NIIMBL eXperience @RaritanValleyCC

Led by Raritan Valley Community College in New Jersey

NIIMBL eXperience @BioKansas

Led by BioKansas in the Kansas and Missouri region

2023 NIIMBL eXperience

Based on the program's success and the positive feedback from students and hosts, we looked to expand the NIIMBL eXperience to more students across the country in 2023. Through a competitive application process, we introduced a regional expansion and awarded $200K to launch three new NIIMBL eXperience programs.

In June 2023, Albany College of Pharmacy and Health Sciences (New York) and Raritan Valley Community College (New Jersey) hosted 18 and 12 students, respectively. Both programs featured interactive sessions, facility tours, and networking opportunities with companies in each region.

The final 2023 NIIMBL eXperience was hosted by BioKansas in August. In addition to facility tours and networking, the 10 participants capped off the week by attending Kansas City's popular Innovation Festival, which included technology advancement sessions and live music.

In total, 41 students took part in a NIIMBL eXperience program in 2023, more than doubling the combined total from 2019 to 2022.

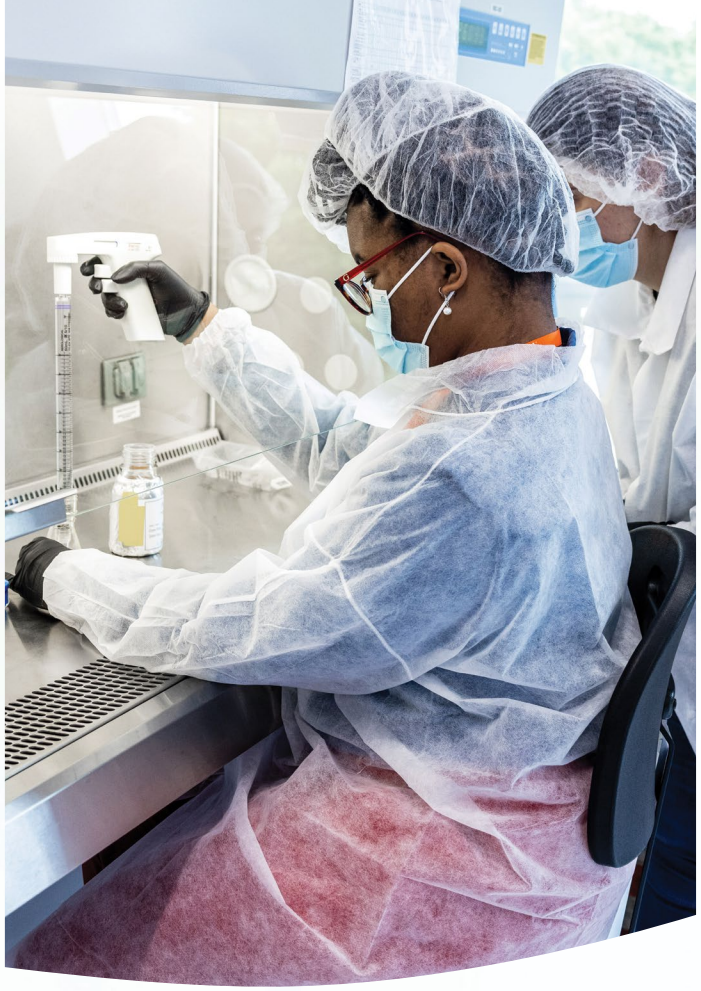
> "Learning about all these biopharmaceutical companies was really helpful for me to get exposure of what STEM fields/paths are out there and how we can make a difference in the world."
>
> NIIMBL eXperience @ RVCC Participant

Workforce Development

TALENT INITIATIVES

NIIMBL is committed to helping connect our industry members and broaden recruiting pipelines for both new and experienced talent.

Our virtual career fairs allow human resources and talent acquisition teams to meet new talent and expand candidate pools. These fairs also enable students and early-career talent to learn more about opportunities that may inform their education or career trajectories.



In 2022-2023, we hosted two virtual career fairs. Between the two events, nearly 500 candidates scheduled more than 1300 meetings with recruiters from 38 companies and educational institutions. Our industry members have spoken highly about the value these events bring by connecting them to new sources of talent—with many of our member companies hiring candidates they met at these events.

During the summer of 2023, NIIMBL conducted listening sessions and focus groups with talent acquisition, human resources, and hiring manager representatives from 15 of our large industry members. Ideas captured during these conversations will continue to inform NIIMBL's talent initiatives as we create new opportunities for the biopharmaceutical manufacturing ecosystem to share best practices and build new relationships that support hiring a world-class workforce.

"I think the entire experience gave me courage and an exceptional look into the real world of engineering and science. I've never been able to get exposure to these facilities and devices, and I think understanding the background of the people clad in lab coats and what they studied helped give me more options and hope that I can find my path while I study."

NIIMBL eXperience @ ACPHS Participant

Workforce Development

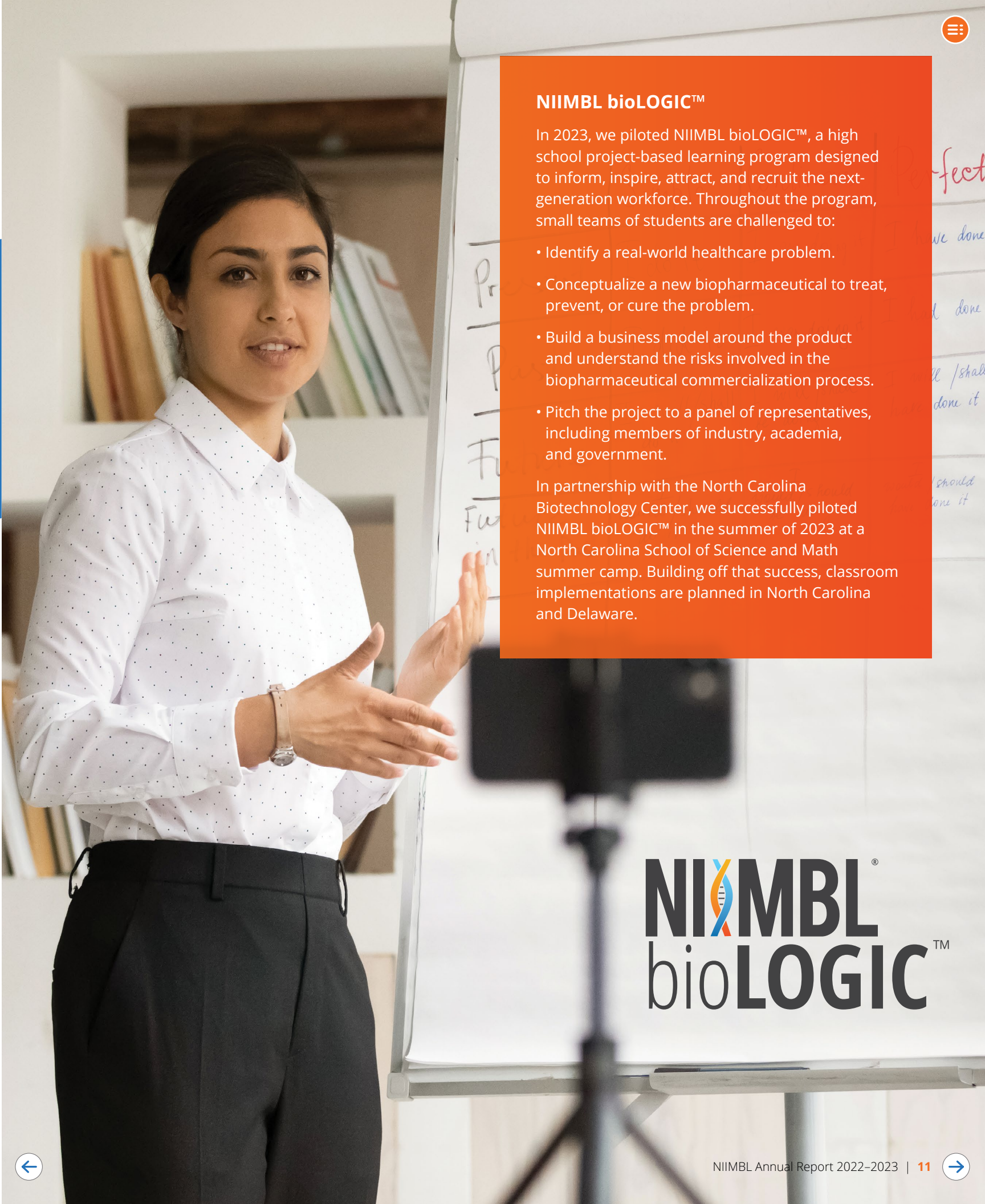
NIIMBL Faculty Fellows Program

In December 2022, we announced the **first participant of the NIIMBL Faculty Fellows Program, Dr. Sarah Harcum** from Clemson University. Dr. Harcum will share her cell culture expertise with the Process Intensification Test Bed Design team and gain practical experience in protein purification.

Sarah Harcum, Ph.D.
Clemson University

First participant of the
NIIMBL Faculty Fellows Program

The NIIMBL Faculty Fellows Program aims to facilitate collaboration between academics and industry. Faculty Fellows will gain valuable experience in state-of-the-art biopharmaceutical manufacturing, learn about real-world industry challenges, and seed new industry-academic partnerships.



NIIMBL bioLOGIC™

In 2023, we piloted NIIMBL bioLOGIC™, a high school project-based learning program designed to inform, inspire, attract, and recruit the next-generation workforce. Throughout the program, small teams of students are challenged to:

- Identify a real-world healthcare problem.
- Conceptualize a new biopharmaceutical to treat, prevent, or cure the problem.
- Build a business model around the product and understand the risks involved in the biopharmaceutical commercialization process.
- Pitch the project to a panel of representatives, including members of industry, academia, and government.

In partnership with the North Carolina Biotechnology Center, we successfully piloted NIIMBL bioLOGIC™ in the summer of 2023 at a North Carolina School of Science and Math summer camp. Building off that success, classroom implementations are planned in North Carolina and Delaware.

NIIMBL® bioLOGIC™

NIIMBL-led Programs & Projects

Re-imagining the manufacture of life-saving medicines

NIIMBL-led Programs and Projects bring together experts from industry, academia, and government to create a future vision of biopharmaceutical manufacturing. Organized around a common theme, these Programs and Projects address current challenges and accelerate the development of new technologies, enabling more efficient and safe manufacturing processes for life-saving medicines. In 2022-2023, we continued to advance our established programs and moved closer to launching new programs in key areas.

Process Intensification

The goal of our Process Intensification Program is to improve biopharmaceutical manufacturing by developing and commercializing technologies that enhance flexibility, promote sustainability, maintain process control, and reduce costs. The Program includes 17 organizations collaborating in five workstreams: Integration, Sustainability, Control Strategy, Flexibility, and Test Bed Design. In 2022-2023, the team developed a baseline state-of-the-art facility layout and built a test bed at NIIMBL headquarters. The test bed will allow for technology evaluation, comparison, and demonstration.

Other key accomplishments include:

- Demonstrating inter-system software interchangeability and re-configurability for improved flexibility.
- Developing easy-to-use sustainability models, including a sustainability glossary and waste process map.
- Creating strategies to control microbes during production to minimize contamination and reduce recovery time.

Biomanufacturing Readiness Levels (BRL)

In September 2022, we published the Biopharmaceutical Manufacturing Readiness Levels (BRL)[1] guidance document in the journal *Biotechnology and Bioengineering*. The BRL is a structured framework to assess technology maturation from concept to commercialization in a biomanufacturing setting. Manufacturing Readiness Levels were first published by the Department of Defense. However, the BRL is the first guide tailored to the biopharmaceutical industry. The goal is to develop a shared vocabulary for technology innovators, developers, and end users to assess gaps and risks associated with implementing a new technology in clinical and commercial manufacturing of a biopharmaceutical product. In addition to the publication, we developed an online self-assessment platform for academics, small- to medium-sized manufacturers (SMMs), and large industry representatives to evaluate their technology according to the BRL guidelines. We rolled out the framework at the National Meeting in June 2023 and received constructive feedback. We will continue to refine this collaborative framework for new technology evaluation to support development and manufacturing of biopharmaceutical products.

[1] Kedia, S. B., Baker, J. C., Carbonell, R. G., Lee, K. H., Roberts, C. J., Erickson, J., Schiel, J. E., Rogers, K., Schaefer, G., & Pluschkell, S. (2022). Biomanufacturing readiness levels [BRL]—A shared vocabulary for biopharmaceutical technology development and commercialization. Biotechnology and Bioengineering, 119, 3526–3536. https://doi.org/10.1002/bit.28227

Vaccine Manufacturing and Analytical Characterization

The goal of our Vaccine Manufacturing and Analytical Characterization Program is to accelerate production of innovative vaccines through the implementation of new manufacturing technologies and product characterization technologies. The Program seeks to address shared workforce and technology challenges, enhancing the capabilities of U.S.-based and global vaccine manufacturers. It encompasses and builds upon our current vaccine work supported by the Bill & Melinda Gates Foundation and the American Rescue Plan. This year, we took significant steps toward the Program's goal. We selected and obtained key instrumentation and equipment for our Vaccine and Analytics and Assays Center at NIIMBL headquarters, funded through the American Rescue Plan. A Scoping Workshop was held in March 2022 with key stakeholders in the vaccine manufacturing ecosystem to establish parameters for the Program.

Big Data

Our Big Data Program enables biomanufacturers to harness the power of data to make informed decisions in real time. The Program aims to create standards that meet the industry's need for a shared consensus on data-related areas. One of the key initiatives within the Big Data Analytics Program is the development of the Biopharmaceutical Manufacturing Ontology (BPMO) platform. The BPMO will define the properties and relationships of concepts, enabling data engineers to efficiently capture and more readily access and transfer relevant data about the process. The open-source platform will ensure broad access across the industry and allow for continued modifications and expansion. The BPMO promises to be a game-changer as our industry looks to use data to gain deeper insights into manufacturing processes. In addition to the BPMO, the Program is looking ahead to other areas in which it could provide value to the industry. In March 2023, more than 100 representatives from the biopharmaceutical and data sciences communities took part in a Big Data Roadmapping Workshop. The goal of the workshop was to identify industry needs and prioritize areas for future work. The Program plans to launch new projects based on this roadmap.

NIIMBL-led Programs & Projects

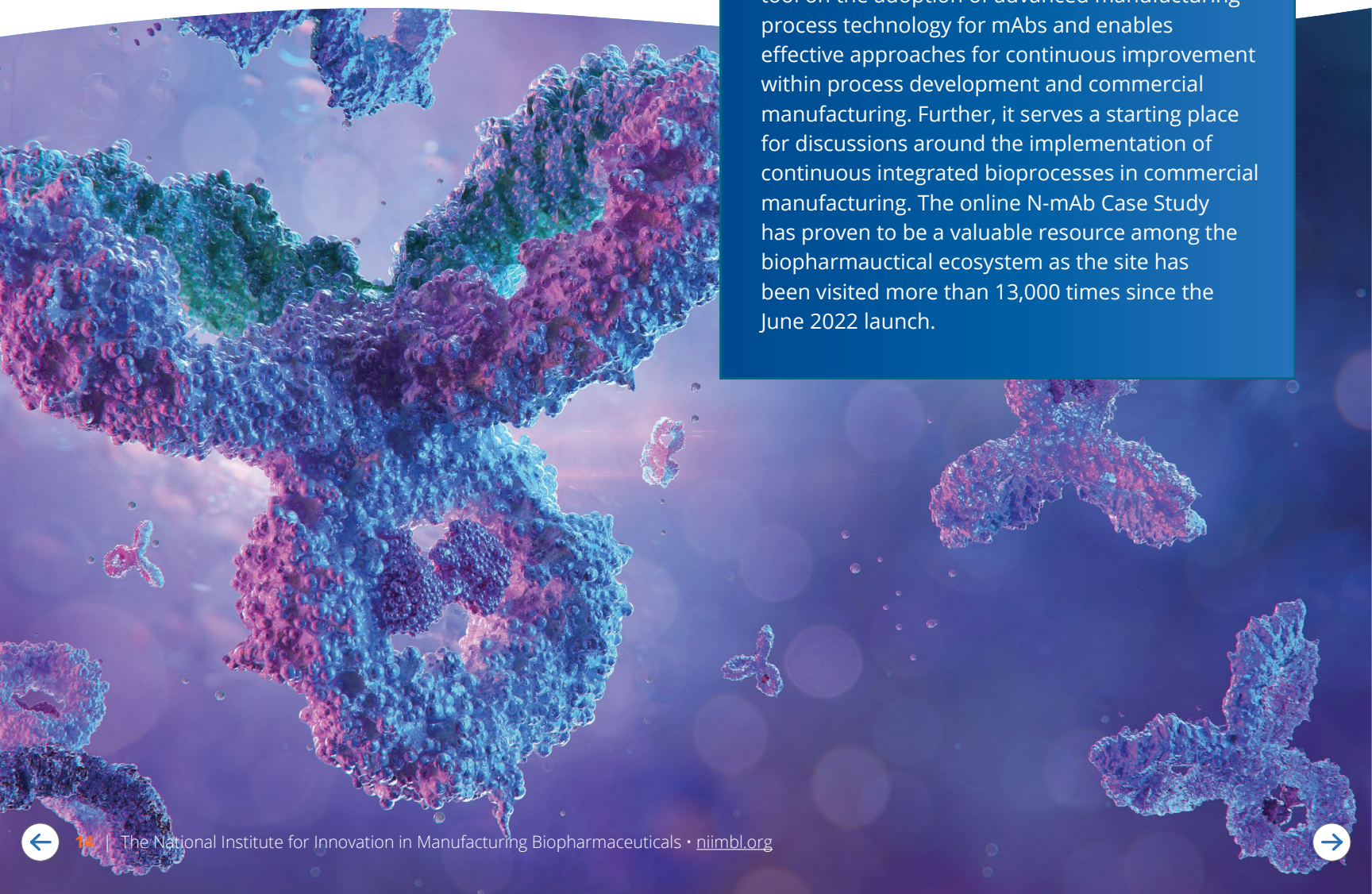
Viral Vector Manufacturing and Analytics

Preparations continued for our Viral Vector Manufacturing and Analytic Program launch. The Program's mission is to develop a robust, economically viable, shared-access platform for the technical development, manufacturing, and characterization of adeno-associated virus (AAV)-based gene therapy vectors. These advancements will enable gene-based therapies capable of serving the full spectrum of patient needs, from prevalent indications to ultra-rare diseases, without cost or speed limitations. Through workshops and discussions with key stakeholders within the NIIMBL and gene therapy communities, the team identified AAV vectors as the Program's focus. The Program includes two workstreams: process and analytics. The Process workstream aims to develop broadly available, robust, and replicable AAV manufacturing process as well as drive and demonstrate process capabilities to AAV gene therapy applications.

The Analytics workstream will develop and disseminate AAV analytical capabilities for characterization, batch release, and stability monitoring. Additionally, the workstream will support the availability and utilization of standards, reference materials, and data.

N-mAb

In June 2022, we published our online N-mAb Case Study. With contributions from more than 60 industry and government stakeholders from 20 organizations, N-mAb provides shared expectations and vocabulary around a control strategy for an integrated continuous bioprocess for a hypothetical monoclonal antibody. The Case Study provides a teaching and learning tool on the adoption of advanced manufacturing process technology for mAbs and enables effective approaches for continuous improvement within process development and commercial manufacturing. Further, it serves a starting place for discussions around the implementation of continuous integrated bioprocesses in commercial manufacturing. The online N-mAb Case Study has proven to be a valuable resource among the biopharmauctical ecosystem as the site has been visited more than 13,000 times since the June 2022 launch.



American Rescue Plan

Strengthening the nation's capacity to meet coronavirus-related public health challenges

With diverse expertise across our community, NIIMBL is well-positioned to develop innovations that will help the nation prevent, prepare for, and respond to coronavirus public health threats. In December 2021, we awarded 32 projects to member organizations across the U.S., funded through the American Rescue Plan (ARP). As of June 2023, members completed 11 of these ARP projects, with additional projects scheduled to finish in 2024. The ARP projects address key areas such as vaccine production, antigen scaling, mobile plasmid Good Manufacturing Practice capabilities, and workforce development. In addition, six projects established testbeds to support collaborative innovation at NIIMBL.

Project Highlight

Helping community colleges meet workforce demand in cell and gene therapeutics

Workforce Expansion in Biomanufacturing Emerging Technologies (WEBET)

MONTGOMERY COUNTY COMMUNITY COLLEGE, BLUE BELL, PA

TYPE:

Academic Research Institution

PARTICIPATING ORGANIZATIONS:

Solano College (CA), MiraCosta College (CA), Quincy College (MA), Forsythe Tech (NC), Shoreline College (WA)

INDUSTRY NEED

The discovery and development of new cell- and gene-based therapies has led to an almost exponential growth of the industry—and a clear need for a workforce trained in the biomanufacture of these new therapies. Many community colleges have existing programs that focus on biomanufacturing of traditional protein-based therapeutics, but they needed guidance on how to expand their programs to include the skills and knowledge related to cell and gene therapies.

SOLUTION

Faculty from six community colleges came together to form the WEBET collaborative to address the need for workforce training programs to support the growing cell and gene therapy industry. Their goal was to develop materials and guidance to help community colleges incorporate training for bioprocessing of cell and gene therapies into their existing courses and programs.

WEBET hired an expert in labor market analysis to better understand the cell and gene therapy industry's workforce needs. They also conducted a series of six listening sessions with hiring managers and subject experts from 28 companies, including Kite Pharma, Thermo Fisher, ViaCyte, A2 Biotherapeutics, UCSD, Bristol Myers Squibb, Lyell, and Seagen. The listening sessions produced a wealth of information about the topics and skills to be included and the types of equipment needed for a cell and gene therapy lab-based curriculum.

WEBET members met over the course of a year to develop skill standards, course outlines, and hands-on lab modules that could be adopted by community college faculty. Standard operating procedures for two lab modules on AAV production and QC were developed. WEBET also held two train-the-trainer sessions on the new materials to provide guidance on implementation; the sessions were attended by more than 130 participants from academic institutions.

"Through NIIMBL funding and connections, we generated resources that will be useful for hopefully hundreds of community colleges and training programs across the country."

Maggie Bryans,
Montgomery County Community College

OUTCOME

Project partner colleges expanded their programs to include cell and gene therapy, with Solano College developing a new certificate program and Montgomery County Community College, Quincy College, and MiraCosta College developing a new course in cell and gene therapy.

In addition, the materials and resources developed by WEBET are being incorporated into courses at Frederick Community College and Montgomery College in Maryland, Santa Monica College and Compton College in California, Collin College in Texas, and Alamance Community College in North Carolina. All of the program materials, including the workforce analysis and train-the-trainer videos, have been made available on the Northeast Biomanufacturing Center and Collaborative (NBC2) website. An enduring impact of the WEBET project has been the growth of the academic-industry network, which continues to meet yearly to discuss curriculum development.

This project was developed with an award from the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) and financial assistance from the U.S. Department of Commerce, National Institute of Standards and Technology (70NANB17H002).

Project Highlight

Reducing waste and cost by rethinking the antibody manufacturing process

Single-Use Modules for Continuous Removal of Antibody Fragments

NORTH CAROLINA STATE UNIVERSITY, RALEIGH, NC

TYPE:

Academic Research Institution

PARTICIPATING ORGANIZATIONS:

Ligatrap, Merck & Co., Inc., MilliporeSigma, Rensselaer Polytechnic Institute (RPI)

INDUSTRY NEED

In the manufacture of therapeutic antibodies, bioreactors produce the antibody product within a "soup" of spent reagents, waste products, cells, fragments of cells, and pieces of antibodies. The current approach to removing these impurities involves capturing the antibody product and washing away the impurities through a series of chromatography, filtration, and centrifugation steps, each of which requires its own set of tanks, reagents, water streams, controls, and analytics. Streamlining and simplifying the impurity removal process would have an enormous impact on reducing waste, particularly water usage, ultimately reducing manufacturing costs.

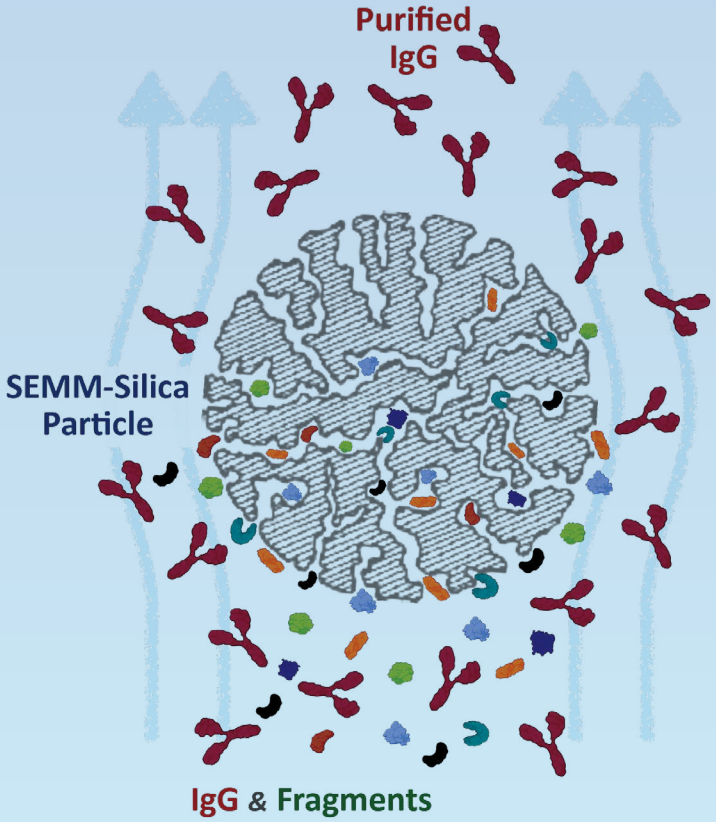
SOLUTION

Stefano Menegatti at North Carolina State University and Steven Cramer at RPI discussed flipping the impurity removal process: instead of capturing the antibody product, it might be possible to capture the impurities and let the antibody continue through the process, similar to what is done in pharmaceutical manufacturing. This "flow-through" approach would simplify the removal of impurities and reduce the number of steps and resources needed to produce a safe therapeutic antibody product.

Working with Ligatrap and Michael Phillips at MilliporeSigma, the team focused on removing antibody fragments that can cause off-target effects in patients. The team developed a porous material out of inexpensive silica and embedded chromatographic particles in the pores to bind antibody fragments. As the "soup" from the bioreactor flows through the material, smaller antibody fragments enter the pores, are captured, and remain bound, leaving the antibody product behind.

"Flow-through methods to remove impurities during therapeutic antibody manufacturing reduce the use of natural resources and energy, lower costs, and ultimately expand access to these life-saving products."

Stefano Menegatti, PhD,
North Carolina State University



OUTCOME

To test the new technology, MilliporeSigma, Merck, and KBI Biopharma provided more than 50 bioreactor mixtures of various compositions that were fed through the porous silica prototype.

With optimization, the new material was able to reduce the antibody fragments in the mixtures to between 1% and 3% of the starting concentration.

The new flow-through technology represents a radical redesign of the current approach to impurity removal in therapeutic antibody manufacturing. In addition, the technology can be applied to the manufacturing of other biological therapeutics, simply by changing the capture antigens within the pores.

This project was developed with an award from the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) and financial assistance from the U.S. Department of Commerce, National Institute of Standards and Technology (70NANB17H002).

Project Highlight

Real-time, direct analysis of vaccine stability with NMR imaging

Noninvasive Process Analytical Technology (PAT) for Aluminum-Adjuvanted Vaccines

UNIVERSITY OF MARYLAND BALTIMORE, BALTIMORE, MD

TYPE:

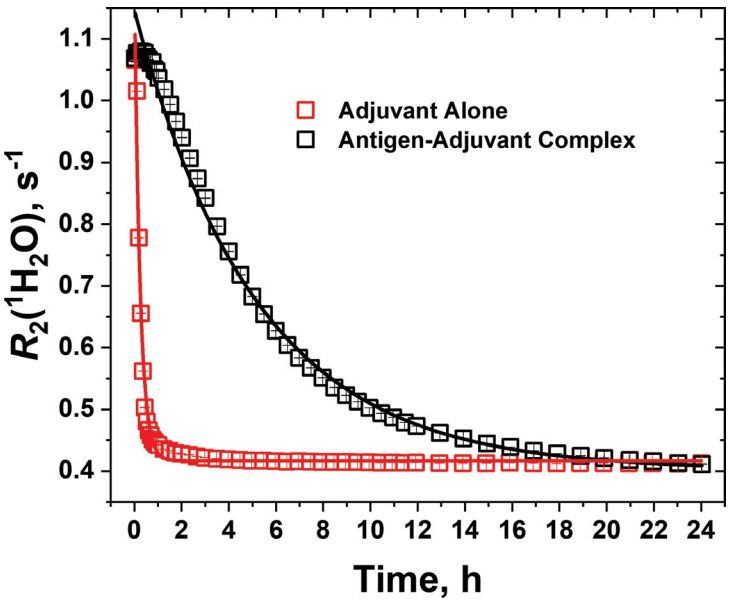
Academic Research Institution

PARTICIPATING ORGANIZATIONS:

Merck & Co., Inc., Pfizer Inc.

INDUSTRY NEED

Vaccines often contain adjuvants that help boost the effectiveness of the antigen in stimulating an immune response. Analyzing the stability of adjuvanted vaccines is critical but challenging for several reasons. Adjuvanted vaccines are non-transparent suspensions, and some adjuvants, such as aluminum, can clump together and settle at the bottom of the vial, which interferes with analysis. The vaccine suspension often must be diluted before testing, which introduces the risk of contamination as vials are opened. Some vaccines must be further treated before they can be analyzed, so the vaccine is no longer in its "native" state. These issues are even more complex for vaccines that contain more than one antigen. New noninvasive approaches were needed that could analyze adjuvanted vaccines without tampering or changing the vaccine, and that could be done in real time.



SOLUTION

Led by Bruce Yu, PhD, a team of researchers at University of Maryland Baltimore (UMB) partnered with Merck and Pfizer to evaluate whether nuclear magnetic resonance (NMR) imaging could be used for noninvasive analysis of vaccines containing aluminum adjuvants. NMR can be performed directly on vaccine suspension in vials, without the need for dilution or manipulation. The antigen-adjuvant complex is an active pharmaceutical ingredient (API) of aluminum-adjuvanted vaccines. When antigen is adsorbed to the surface of the aluminum adjuvant, the sedimentation process occurs very quickly. NMR imaging is also fast, with data collected in less than a minute, so it can provide a real-time snapshot of information about the vaccines and antigen-adjuvant interactions.

Benchtop NMR Facility for PAT Development

OUTCOME

NMR was able to noninvasively detect the adsorption of antigens to adjuvant—an important critical quality attribute (CQA) of aluminum-adjuvanted vaccines. The team compared the ability of their wNMR technique to conventional process analytical techniques to measure the effects of gravitation, flow, and freezing/thawing on antigen-aluminum adjuvant interactions in vaccine samples. wNMR analysis performed at UMB produced similar information as conventional techniques performed at Merck and Pfizer.

By removing the need for sample preparation, wNMR saved 1 hour of time for every 3 samples analyzed.

Minimizing the hands-on steps also reduced the risk of analyst error or sample alteration. While further analysis is needed, the wNMR approach could significantly cut the cost of reagents, equipment, and resources needed for analysis of adjuvanted vaccines.

Through this collaboration, Merck and Pfizer were able to draw on the deep knowledge of wNMR at UMB and find new ways to improve process analytics. In turn, Dr. Yu's team at UMB had their innovative NMR technology independently verified by industry and confirmed that their research was filling an industry need.

"By working with industry, we're able to answer their scientific questions and independently validate the benefits of our technology – it's a win-win situation."

Bruce Yu,
University of Maryland Baltimore

This project was developed with an award from the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) and financial assistance from the U.S. Department of Commerce, National Institute of Standards and Technology (70NANB17H002).

Project Highlight

Using real-world simulations to train the biomanufacturing workforce

Modularized PAT Online Training Platform to Accelerate Workforce Innovation in Biopharmaceuticals Manufacturing

NORTHEASTERN UNIVERSITY, BOSTON, MA

TYPE:

Academic Research Institution

PARTICIPATING ORGANIZATIONS:

Massachusetts Institute of Technology, Genentech, Merck & Co., Inc., Janssen, Sartorius

INDUSTRY NEED

There is an enormous demand for biomanufacturing workforce development, both at the academic level and to keep the current workforce up to date with new technologies and skills. Hands-on training is slow, expensive, and insufficient to meet the needs of the rapidly growing biopharmaceuticals industry. Investigators at Northeastern University and the Massachusetts Institute of Technology collaborated to develop more flexible, scalable, and cost-effective approaches to biomanufacturing workforce training.

"The digital twin platform facilitates large-scale workforce development on end-to-end bioprocessing in a low-cost virtual environment."

Wei Xie, PhD,
Northeastern University

SOLUTION

The team turned to the concept of a "digital twin," a computer program that uses real-world data to re-create processes—in this case, biopharmaceutical manufacturing—as virtual simulations. The digital twin approach allows users to explore realistic variations in the biopharmaceutical manufacturing process and test solutions to problems safely and inexpensively in a virtual environment. Simulations are run and the results analyzed within much shorter timeframes than real-world experiments. The digital twin platform also powerfully demonstrates how a small error in one part of the process can propagate through the entire process.

To apply a digital twin platform to workforce training, the team worked closely with industry partners to understand their specific training needs and develop case studies. The industry partners provided real-world data that was fed into the digital twin platform to create simulations with realistic levels of variability and uncertainty. The entire process—from the bioreactor to the purification columns—was recreated virtually, along with an interactive interface and data visualizations similar to that used in industry. The team also developed lesson plans for using the simulation to learn about troubleshooting, risk analysis, and process control.

OUTCOME

By allowing students to learn in a virtual environment, the digital twin makes it possible to train more students, train them better, and at a lower cost.

It can be applied to any number of biomanufacturing processes. The platform components are open, and manufacturers can feed their own data into the digital twin to tailor the simulations to their specific workforce training needs.

The digital twin software and the lesson plans have already been introduced in workshops and are currently being integrated into courses at both Northeastern University and MIT and used to develop a modeling course at MIT for a new degree program with a focus on biomanufacturing. All the materials are available upon request through the project principal investigators at the Biopharmaceutical Analysis Training Lab (BATL) at Northeastern University and Bioprocess Data Analytics and Machine Learning at MIT.

This project was developed with an award from the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) and financial assistance from the U.S. Department of Commerce, National Institute of Standards and Technology (70NANB17H002).

Project Highlight

Real-time live virus quantitation to optimize production and minimize waste

Virus Quantitation by Laser-Force Cytology™ of Bioreactor Samples

CARNEGIE MELLON UNIVERSITY, PITTSBURGH, PA

TYPE:

Academic Research Institution

PARTICIPATING ORGANIZATIONS:

LumaCyte, Inc., Merck Sharp & Dohme LLC, Rensselaer Polytechnic Institute (RPI)

INDUSTRY NEED

In the biopharmaceutical industry, the urgent need for rapid and sensitive virus detection during the production of viral vaccines has become increasingly critical. Current methods to quantify functionally active virus capable of infecting a cell (viral titer)—such as TCID50 and plaque assays—are time intensive, labor intensive, error prone, and highly subjective. With these current assays, the cost of viral contamination events can be in the hundreds of millions of dollars due to lost product, lost sales, and ultimately a shortage of drug supply to the patients who need it most. For live virus vaccines, regulators have called for real-time, objective, in-process analytics to reduce variability and ensure product safety and consistency. New methods that are capable of more rapid but still broad, sensitive detection of virus are highly desirable, providing the potential to reduce out-of-specification events that lead to batch failures, thereby saving time and costs.

SOLUTION

Working closely with Merck, the team set out to measure viral titers from three angles. LumaCyte's Radiance® instrument, which leverages an advanced optical and microfluidic technology called Laser Force Cytology™, has the ability to analyze and measure changes in various physical and chemical properties induced by infectious virus at the single-cell level, including optical force, shape, and stiffness. Here, LumaCyte applied the LFC™ method to adherent cells on microcarriers for use in viral vaccine production culture processes, precisely quantifying the amount of functional virus in bioreactor samples in a fraction of the time needed by current assays. To confirm the identity of the virus in the bioreactor sample, Dr. Schneider at Carnegie Mellon developed a method of capillary electrophoresis using genetic probes that bind to specific viral genomes and produce a detectable shift in the sample. Finally, team members at RPI utilized bioreactor data to develop mathematical models to predict the number of uninfected, infected, and dead cells in the bioreactor at any point in the production process.

This project was developed with an award from the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) and financial assistance from the U.S. Department of Commerce, National Institute of Standards and Technology (70NANB17H002).

OUTCOME

Merck invited the team to their facility to quantify infective, fluorescently tagged measles virus in bioreactor samples.

The team produced a working prototype that could measure viral titer in bioreactor samples in minutes, compared to several weeks with viral culture, producing results that correlated with existing assay results.[1]

Capillary electrophoresis accurately detected functional virus down to femtomolar levels. Ultimately, the team envisions that virus and cells sampled from the bioreactor could be analyzed in real time in two separate streams, one to measure the quantity of virus and the other to measure virus infectivity.

"Our project demonstrated that NIIMBL is nimble. It brought together partners to identify and pursue priorities and take the research in the direction that would ensure that industry needs were met."

Sean Hart, PhD
CEO and CSO, LumaCyte, Inc.

[1] McCracken, R., Al-Nazal, N., Whitmer, T., Yi, S., Wagner, J. M., Hebert, C. G., Lowry, M. J., Hayes, P. R., Schneider, J. W., Przybycien, T. M., Mukherjee, M. (2022). Rapid in-process measurement of live virus vaccine potency using laser force cytology: Paving the way for rapid vaccine development. Vaccines, 10, 1589. http://doi.org/10.3390/vaccines10101589

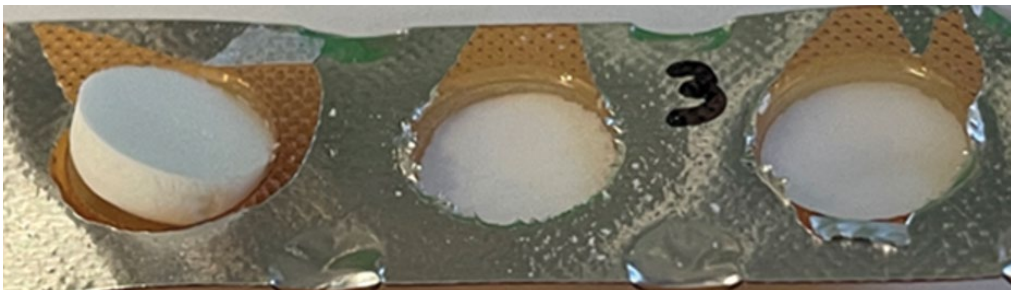
Project Highlight

Removing barriers to vaccine distribution

Development of a Thermo-Tolerant, Multidose, Egg-Produced, Vector-Based Coronavirus Vaccine

PATH VACCINES AND PHARMACEUTICAL TECHNOLOGIES, SEATTLE, WA

TYPE:
Non-profit Organization



INDUSTRY NEED

Currently available coronavirus vaccines must be kept refrigerated or frozen to ensure they remain stable and effective. Keeping vaccines cold as they move from the manufacturer to the clinic relies on a continuous series of refrigerated buildings, vehicles, and equipment—together referred to as cold chain infrastructure—that is both highly complex and expensive. The requirement for cold chain infrastructure limits the distribution of vaccines, particularly to low-resource and rural areas. In addition, the need for refrigeration limits vaccine stockpiling as well as the ability to transport vaccines locally, which leads to vaccine waste.

SOLUTION

Dr. Manjari Lal's team at PATH set out to formulate a heat-tolerant COVID-19 vaccine that would be stable at room temperature or higher for extended periods of time. They developed both liquid and dry formulations of a vector-based COVID-19 vaccine candidate, NDV-HXP-S. The vaccine was originally developed at the Icahn School of Medicine at Mount Sinai and University of Texas at Austin, and was found to be effective, safe, and potent in preclinical and clinical studies. Dr. Manjari's team tested the ability of each vaccine formulation to remain stable—based on the amount of vaccine antigen remaining—after storage at various temperatures over a 6-month period.

OUTCOME

The liquid formulation was stable at 2-8°C (35-46°F) and 25°C (77°F) for up to 6 months, whereas the dry (lyophilized) formulation remained stable at temperatures up to 40°C (104°F) for 6 months. The team also developed a sublingual tablet formulation for needle-free vaccine administration, which maintained stability at 40°C for 4 weeks.

Heat-tolerant vaccines eliminate the need for and expense of cold chain infrastructure, which not only expands distribution to hard-to-reach communities but also potentially reduces the cost of the vaccines themselves.

New, needle-free formulations continue to be an area of active research that opens up additional opportunities for improving ease-of-use, reducing costs, and achieving equity in vaccine access.

"Vaccine manufacturers must work to make vaccines thermostable to improve access and reduce costs."

Manjari Lal, PhD,
PATH Vaccines and Pharmaceutical Technologies

Stability over 6 months

25°C (77°F)

LIQUID

40°C (104°F)

DRY (LYOPHILIZED)

This work was performed under a Project Award Agreement from the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) and financial assistance award 70NANB21H085 from the U.S. Department of Commerce, National Institute of Standards and Technology.

Project Highlight

Producing stable vaccines to improve access

Development of Scalable, Thermostable, Spray Dried Vaccine Formulations Applicable for Coronavirus Vaccines

FRAUNHOFER USA, NEWARK, DE

TYPE: Non-profit Organization

R&D-scale spray dryer of the general type used for the project

INDUSTRY NEED

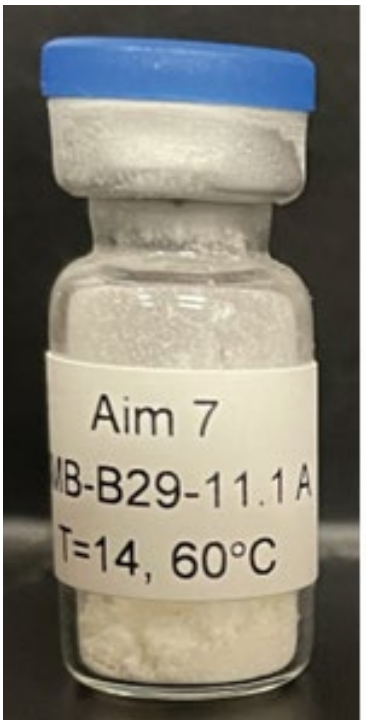
Most licensed vaccines are liquid formulations that require cold storage and transport, which limits their distribution. Dry formulations are more stable at higher temperatures, but the current process—lyophilization—is time- and energy-intensive and can alter vaccine structure and function. Spray drying is the leading alternative approach to generating dry vaccine formulations. Not only is it less expensive than lyophilization, but it is also scalable and can be run in-line with other downstream processes.

> "Compared to lyophilization, spray drying is a rapid, controllable, single-step process that reduces time and energy consumption."

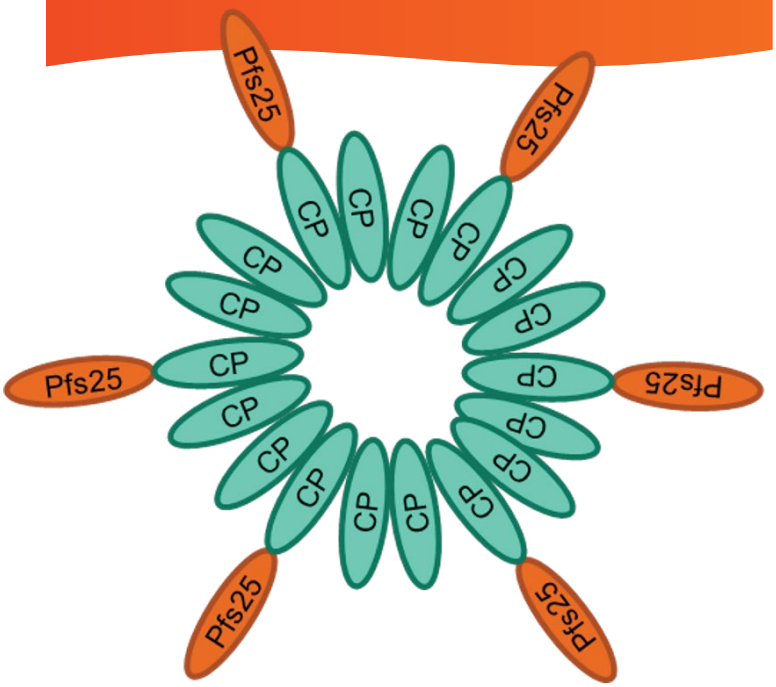
Stephen Streatfield, PhD,
Fraunhofer USA

SOLUTION

The team at Fraunhofer investigated various conditions and components for spray drying two types of vaccines: a protein subunit vaccine of the SARS-CoV-2 receptor binding domain (RBD) and a more complex virus-like particle (VLP) vaccine for malaria. They generated the RBD and VLP vaccine antigens with a range of excipients, buffers, adjuvants, and spray drying conditions and temperatures and performed stability studies at storage temperatures of up to 60°C for 14 days. Through several rounds of testing, the team aimed to find the most stable and reproducible spray dried vaccine formulations. As some commonly used assays were incompatible with specific excipients or adjuvants, the team also developed alternative assays for selection of the most stable formulation components.



Schematic of virus-like particle (VLP) displaying a vaccine antigen



OUTCOME

An initial set of 24 different formulations of the RBD and VLP vaccines were generated. Three rounds of testing and improvements narrowed down the field to three candidates of the RBD and VLP vaccines that were stable at up to 60°C and 37°C, respectively, for 2 weeks.

The results showed that spray dried product, which is less expensive and quicker to produce, meets a stability standard comparable to the lyophilized product.

Next steps include extending stability testing of the lead spray dried vaccine candidates to 30 days at up to 60°C for the RBD vaccine and up to 37°C for the VLP vaccine. The team will also test the immunogenicity and protective efficacy of the lead spray dried vaccine formulations in animal models. Future studies will examine other components for spray dried formulations, and apply spray drying to other vaccines, such as a VLP-based COVID-19 vaccine.

This work was performed under a Project Award Agreement from the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) and financial assistance award 70NANB21H085 from the U.S. Department of Commerce, National Institute of Standards and Technology.

Project Highlight

Clearing the air of SARS-CoV-2

A New Generation of High-Efficiency HVAC Filters That Can Be Used With Existing Infrastructure to Stop The Spread of Coronavirus Through Recirculation of Air

NORTH CAROLINA STATE UNIVERSITY, RALEIGH, NC

TYPE: Academic Research Institution

INDUSTRY NEED

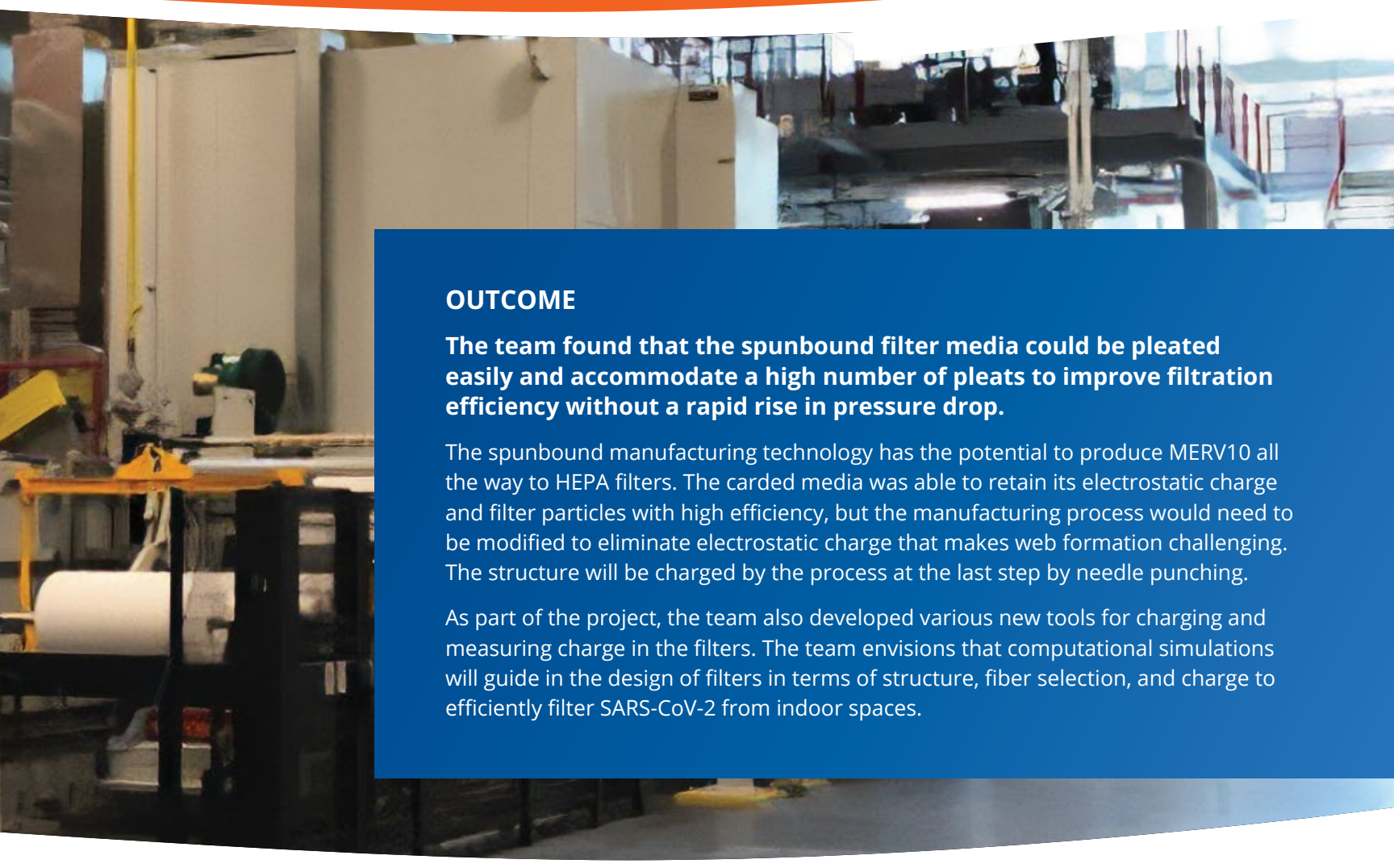
Filtration of SARS-CoV-2 virus out of indoor air remains an ongoing challenge in reducing the transmission of COVID-19. As a filter removes particles from the air (particle loading), it becomes more difficult for air to pass through, leading to a pressure drop and loss of efficiency. To remove coronavirus, filters must be able to capture anything less than a micron in diameter. While MERV13 filters capture coronavirus, current residential air filtration systems are not powerful enough to counteract the pressure drop that occurs with virus particle loading. The goal in filter design is to optimize this tradeoff; for example, adding pleats to filters can improve efficiency and reduce the pressure loss.

SOLUTION

Dr. Behnam Pourdeyhimi and his team at NC State developed and tested filters of electrostatically charged nonwoven polypropylene and PLA polymers, manufactured using spunbound technology and staple carded methods. They also conducted a computational study to run microscale (fiber level) and macroscale (pleat level) simulations to guide filter design and manufacturing. Based on the simulations, the team created and tested single- and double-layer pleated filters containing various proportions of polypropylene and PLA polymers.

"We have built a very strong technical foundation and new tools for the manufacture of coronavirus filters suitable for use in homes and businesses."

Hooman Tafreshi, PhD,
North Carolina State University



OUTCOME

The team found that the spunbound filter media could be pleated easily and accommodate a high number of pleats to improve filtration efficiency without a rapid rise in pressure drop.

The spunbound manufacturing technology has the potential to produce MERV10 all the way to HEPA filters. The carded media was able to retain its electrostatic charge and filter particles with high efficiency, but the manufacturing process would need to be modified to eliminate electrostatic charge that makes web formation challenging. The structure will be charged by the process at the last step by needle punching.

As part of the project, the team also developed various new tools for charging and measuring charge in the filters. The team envisions that computational simulations will guide in the design of filters in terms of structure, fiber selection, and charge to efficiently filter SARS-CoV-2 from indoor spaces.

This work was performed under a Project Award Agreement from the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) and financial assistance award 70NANB21H085 from the U.S. Department of Commerce, National Institute of Standards and Technology.

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North Carolina Biotechnology Center

North Carolina Central University

North Carolina Community Colleges Systems BioNetwork

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Oregon Bioscience Association

PATH Center for Vaccines Innovation & Access

Pennsylvania Biotechnology Center - B+labs

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Project Lead The Way

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The Research Foundation for the State University of New York, on behalf of State University of New York Polytechnic Institute

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Delaware Valley Industrial Resource Center

New Jersey Manufacturing Extension Partnership

North Carolina Manufacturing Extension Partnership

ADDITIONAL PARTNERS

National Institute of Standards and Technology

Food and Drug Administration

National Institutes of Health

NIIMBL interacts with several other federal agencies and institutes.

2022-2023 MEMBERSHIP ENGAGEMENT

Academic Research Institutions	48
Community Colleges	25
Industry (Large)	25
Industry (SMM)	96
MEP	4
Non-profit Research Organizations	34
State Government	2
Other	5

239 TOTAL MEMBERS

16% YEAR-OVER-YEAR GROWTH

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adbb Association for the Advancement of Blood & Biotherapies
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alphinity
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North Carolina Central University Founded 1910
NCMEP North Carolina Manufacturing Extension Partnership
NC State University
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NIH
NIPTE The National Institute for Pharmaceutical Technology & Education
Novi Systems
NIST
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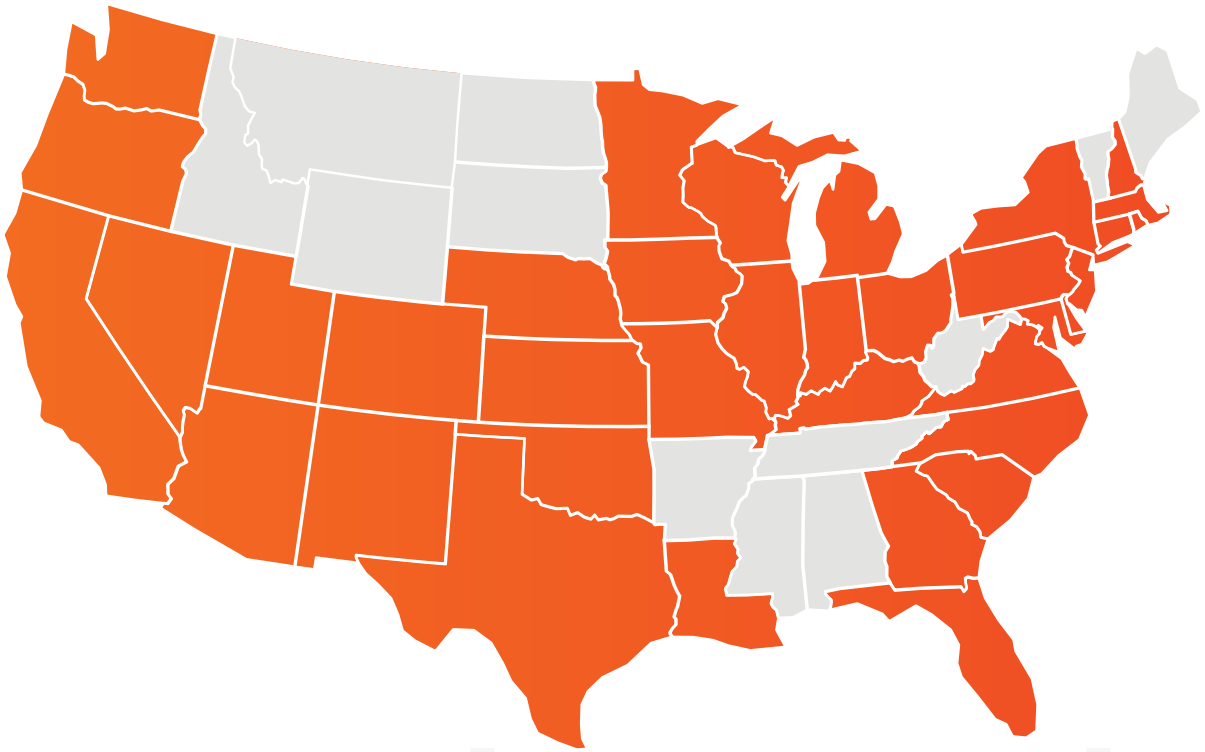
About NIIMBL

The National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) is a public-private partnership whose mission is to accelerate biopharmaceutical innovation, support the development of standards that enable more efficient and rapid manufacturing capabilities, and educate and train a world-leading biopharmaceutical manufacturing workforce, fundamentally advancing U.S. competitiveness in this industry. NIIMBL is part of Manufacturing USA®, a diverse network of federally sponsored manufacturing innovation institutes, and is funded through a cooperative agreement with the National Institute of Standards and Technology (NIST) in the U.S. Department of Commerce with significant additional support from its members.

A NATIONAL NETWORK

NIIMBL's 239 members have operations throughout the U.S.



membership

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